

Breast Cancer

Clinical Trials Resource Guide and Audio Program

A compendium of ongoing and proposed clinical trials
in the neoadjuvant, adjuvant and metastatic settings

Faculty

George W Sledge Jr, MD

Norman Wolmark, MD

Clifford Hudis, MD

Julie R Gralow, MD

John F R Robertson, MD

Edith A Perez, MD

Editor

Neil Love, MD

Contributing Editor

C Kent Osborne, MD



From the publishers of
Breast Cancer[®]
U P D A T E



Download MP3s of this program at BreastCancerUpdate.com/ClinicalTrials

Breast Cancer Clinical Trials Resource Guide and Audio Program

A Continuing Medical Education Activity

Statement of Need/Target Audience

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from clinical trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care, the practicing medical oncologist must be well informed of ongoing and proposed clinical trials, as these offer meaningful therapeutic options to many patients. This CME program is intended to inform and update medical oncologists on breast cancer clinical trials and to encourage their enrollment of appropriately selected patients in these studies.

Global Learning Objectives

- Describe ongoing and planned clinical trials in the adjuvant, neoadjuvant and metastatic settings and counsel appropriately selected patients about the availability of ongoing clinical trials.
- Explain hormonal therapy treatment strategies currently under evaluation for both pre- and postmenopausal patients with ER-positive breast cancer.
- Describe the rationale for and design of ongoing clinical trials of various chemotherapeutic agents, including trials evaluating dose-dense chemotherapy regimens.
- Evaluate treatment strategies combining biologic agents with chemotherapy, endocrine therapy and other biologic agents in planned and ongoing clinical trials.
- Discuss the utility of genomic markers as a tool for determining whether to administer chemotherapy in combination with hormonal therapy for postmenopausal patients with ER-positive breast cancer.
- Describe the results of the large clinical trials evaluating adjuvant trastuzumab in patients with HER2-positive breast cancer as a model for future clinical research.

Purpose of this Breast Cancer Clinical Trials Guide

The purpose of this special edition of Breast Cancer Update is to support these global objectives by offering the perspectives of Drs Sledge, Wolmark, Hudis, Galow, Robertson and Perez on the integration of emerging clinical research data and available clinical trials into the management of breast cancer.

Accreditation Statement

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation Statement

Research To Practice designates this educational activity for a maximum of 4 AMA PRA Category 1 Credit(s)[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

How to Use this CME Activity

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. BreastCancerUpdate.com/ClinicalTrials includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in [blue underlined text](#).

Comments from clinical investigators in this monograph, unless otherwise noted, are from *Breast Cancer Update* and associated audio programs.
Please visit BreastCancerUpdate.com for more.

Table of Contents

I	EDITOR'S NOTE: LET'S GET THIS THING DONE.	3
II	PROLOGUE: THE ADJUVANT TRASTUZUMAB CLINICAL RESEARCH TO PRACTICE MODEL	7
III	CLINICAL TRIALS	13
	Neoadjuvant Therapy	
14	What is the optimal aromatase inhibitor for neoadjuvant therapy? ACOSOG-Z1031	
16	What is the optimal neoadjuvant therapy for women with HER2-negative breast cancer? NSABP-B-40	
	Radiation Therapy	
18	Does partial breast irradiation (PBI) provide equivalent local tumor control compared to whole breast irradiation (WBI) following lumpectomy? NSABP-B-39	
	Adjuvant Endocrine Therapy	
20	What is the optimal adjuvant endocrine therapy for postmenopausal women with DCIS? IBIS-II (DCIS)/NSABP-B-35	
23	What is the optimal duration of adjuvant aromatase inhibitor therapy? NSABP-B-42	
25	Which is the safest and most efficacious aromatase inhibitor as up-front adjuvant therapy for postmenopausal women? CFEM345D2411	
27	What is the optimal adjuvant endocrine therapy for premenopausal patients? SOFT/TEXT/PERCHE	
	Adjuvant Chemotherapy	
30	Which adjuvant bisphosphonate is most effective at preventing metastases? SWOG-S0307	
32	What is the utility of adjuvant chemotherapy for patients with intermediate recurrence scores of the Oncotype DX™ assay? TAILORx	
36	Is oral, single-agent capecitabine as effective as standard adjuvant AC or CMF in older patients? CALGB-49907	
38	What is the optimal chemotherapy regimen for patients with lower-risk node-positive or node-negative disease? CALGB-40101/NSABP-B-36	
40	What is the optimal adjuvant chemotherapy regimen for patients with node-positive or higher-risk node-negative disease? SWOG-S0221	
43	What is the optimal adjuvant chemotherapy regimen for patients with node-positive disease? NSABP-B-38	
46	Is it safe to combine bevacizumab with dose-dense adjuvant chemotherapy? ECOG-E2104	
49	Is bevacizumab a safe and effective treatment for residual disease after preoperative chemotherapy? NCT00121134	
	Metastatic Disease	
51	What is the optimal endocrine therapy for postmenopausal patients with metastases and disease progression on a nonsteroidal aromatase inhibitor? SoFEA/SWOG-S0226/FACT	
54	What is the optimal dosing of fulvestrant for postmenopausal patients? CONFIRM	
56	Does lapatinib improve outcomes when combined with trastuzumab in patients with HER2-positive metastatic disease? EGF104383/EGF104900	
58	Does bevacizumab add benefit to endocrine therapy for metastatic disease? CALGB-40503 (proposed)	
60	Can HER2 and ER cross-talk be therapeutically exploited by combining fulvestrant and trastuzumab? UCLA-0502057-01	
62	What is the benefit of adding bevacizumab to chemotherapy as first- and second-line therapy? RIBBON 1/RIBBON 2	
IV	FUTURE TRIAL CONCEPTS	65
V	STUDY CONTACTS	71
VI	POST-TEST	74
VII	EVALUATION FORM	75

Content Validation and Disclosures

FACULTY AFFILIATIONS



Julie R Galow, MD

Associate Professor, Medical Oncology
University of Washington and
Fred Hutchinson Cancer Research Center
Seattle, Washington



John F R Robertson, MD

Professor of Surgery
Head of Academic Division of
Breast Surgery
University of Nottingham City Hospital
Nottingham, United Kingdom



Clifford Hudis, MD

Chief, Breast Cancer Medicine Service
Solid Tumor Division
Memorial Sloan-Kettering Cancer Center
New York, New York



George W Sledge Jr, MD

Balve-Lantero Professor of Oncology
Professor of Medicine and Pathology
Indiana University School of Medicine
Indianapolis, Indiana



Edith A Perez, MD

Professor of Medicine
Mayo Medical School
Director, Cancer Clinical Study Unit
Director, Breast Cancer Program, Division
of Hematology and Oncology, Mayo Clinic
Jacksonville, Florida



Norman Wolmark, MD

Professor and Chairman
Department of Human Oncology
Allegheny General Hospital
Professor, Drexel University
College of Medicine
Chairman, National Surgical
Adjuvant Breast and Bowel Project
Pittsburgh, Pennsylvania

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest for themselves (or their spouses/partners) that have been resolved through a peer review process: Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Chris Thomson, MD, MS and Kathryn Ault Ziel, PhD — no real or apparent conflicts of interest to report; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc; Research To Practice receives education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Genentech BioOncology/OSI Pharmaceuticals, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Galow — Consulting Fees: Amgen Inc, Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech Inc, Novartis Pharmaceuticals Corporation, Roche Laboratories Inc; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: Genentech Inc, Roche Laboratories Inc. **Dr Hudis** — Consulting Fees: Amgen Inc, Novartis Pharmaceuticals Corporation, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP, Genentech Inc; Ownership Interest: Genomic Health Inc. **Dr Perez** — Contracted Research: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech Inc, Eli Lilly and Company, Pfizer Inc, Sanofi-Aventis. **Dr Robertson** — Consulting Fees: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation, Pfizer Inc, Schering AG; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation, Pfizer Inc; Contracted Research: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation, Schering AG. **Dr Sledge** — Consulting Fees: Genentech Inc, Roche Laboratories Inc; Contracted Research: Sanofi-Aventis. **Dr Wolmark** — Consulting Fees: Sanofi-Aventis.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.



The optimists among us would like to think that May 16, 2005 was a turning point in oncology research. With George Sledge at the helm of the now legendary ASCO "education session," we all got one hell of an education about the potential of targeted cancer therapy.

George's partner in progress, Kathy Miller, set the tone for this highly memorable afternoon by presenting the first report of successful anti-angiogenic therapy for breast cancer, and the day got better and better as a series of spectacular adjuvant trastuzumab data explosions followed from the NSABP, NCCTG and BIG cooperative groups.

In an instant on that afternoon in Orlando, one of the major questions in breast cancer clinical research was definitively addressed by the impressive results from three well-designed and appropriately powered randomized adjuvant trials. This remarkable event effectively validated the molecular targeted approach to common cancers and substantiated our hope and optimism that this might be the end of the beginning of a successful war on cancer.

Now there are exciting new adjuvant studies in HER2-positive breast cancer being developed,

generally looking to add another biologic like bevacizumab or lapatinib to the recipe and to individualize treatment based on tumor markers such as TOPO II and cMYC. These studies join a panoply of other interesting and worthwhile ongoing clinical investigations in all stages of the disease, and one can cautiously conclude that we have entered a new and exciting era of breast cancer clinical research.

The only problem is that we're still in the dark ages in terms of accruing patients onto trials, and we need to do more than just bitch and moan about it. To contribute to the solution of this critical situation, our CME group, Research To Practice, is again partnering with Dr Kent Osborne, co-director of the San Antonio Breast Cancer Symposium, on a clinical trials education initiative that began in 2001.

This information platform/pep rally focuses on the current generation of ongoing studies and new trial concepts under development. Our goal is to encourage oncologists and other oncology healthcare professionals to increase their already staunch efforts in clinical research and to make a renewed commitment to investigate, participate and educate as follows.

INVESTIGATE

The enclosed breast cancer clinical trials audio program and this print CME guide summarize some of the most important and innovative

current breast cancer clinical trials, and provides additional insights and perspectives into their relevance and significance.

Breast Cancer Clinical Trials Faculty



Harold Burstein, MD, PhD



Aman Buzdar, MD



Julie Gralow, MD



Clifford Hudis, MD



C Kent Osborne, MD
(Contributing Editor)



George Sledge Jr, MD



Norman Wolmark, MD



Neil Love, MD (Editor)

By creating this broad overview, our goal is to provide a concise and easy-to-use method to learn about current clinical trials and to understand not only the research relevance but also the exciting potential benefits to participating patients.

Many common clinical situations in breast cancer have suboptimal available therapeutic options, and after witnessing the trastuzumab miracle, we now clearly understand that studies such as the upcoming Intergroup adjuvant bevacizumab trial (see page 68), as discussed by Dr George Sledge on the audio program, can provide patients with the opportunity to receive promising, relatively nontoxic and otherwise unavailable therapies.

Many other current trials offer potential benefits to participating patients, including SWOG-S0307 (page 30), discussed on the audio program by principal investigator Dr Julie Gralow. This study of three different bisphosphonates in the adjuvant setting has some of the broadest eligibility criteria of any current major breast cancer trial.

The study accepts essentially any patient with invasive disease at high enough risk to receive some form of adjuvant systemic therapy, including endocrine therapy alone. SWOG-S0307 is asking an important question, and there should be absolutely no reason why we can't quickly recruit 6,000 patients to find an answer.

Another exciting aspect of the new generation of breast cancer clinical trials is that tissue correlative studies have now become virtually standard, and studies such as ACOSOG-Z1031 (page 14), which is being led by Dr Matt Ellis, hold the promise of unlocking one of the oldest questions in breast oncology: Why do some patients with ER-positive tumors not respond to endocrine therapy? This simple but spectacular and much-needed study is comparing the three available

aromatase inhibitors — anastrozole, letrozole and exemestane — as neoadjuvant therapy for postmenopausal women with ER-positive tumors.

After years of Drs Mike Dixon and John Robertson telling us about their fascinating neoadjuvant endocrine trials across the Pond, we now have a highly noteworthy North American preop endocrine trial, and this study is just a prelude to a planned follow-up protocol that will compare neoadjuvant chemotherapy to the best AI (or dealer's choice if no differences show up in the current study). Vegas is currently booking the AIs over chemo with three points.

The new generation of trials is also asking a number of questions with enormous practical implications in terms of safety and quality of life. For example, after new data sets were presented at ASCO 2006 on cardiac toxicity associated with adjuvant anthracyclines, clinicians are now thinking twice about even four cycles of AC for patients with cardiovascular risk factors such as hypertension.

Help could be on the way in the form of several ongoing adjuvant trials investigating nonanthracycline regimens. My favorite is CALGB-40101, which compares dose-dense paclitaxel to dose-dense AC. Oncologists and cardiologists are keeping their fingers crossed that four cycles of paclitaxel with growth factors might provide adequate efficacy with a better safety profile for patients at lower risk.

To assist San Antonio attendees in keeping clinical research top of mind, another facet to this education initiative is our "protocol water bottles," which will be distributed at the Clinical Trials education booth in Hall C. While staving off dehydration during the long daily sessions, imbibers are encouraged to give some thought to the available study designs.

PARTICIPATE

With the hope that increasing exposure and discussion of clinical trials might be helpful, and to spice things up a bit, we are proud to announce the first annual "Design A Breast Cancer Clinical Trial Challenge." This unique contest — dubbed by Hal Burstein as the "American Idol" approach to protocol design — is rather simple in concept: All you need to do to enter is propose a theoretical protocol that you believe would be worthwhile to implement. (See next page.)

An elite panel of judges will deliberate the merits of each entry and will select five winners.

The authors of the victorious trial designs will be invited to participate in a special audio-recording roundtable and stone crab feast hosted in balmy Miami in February 2007. The edited audio proceedings from that discussion will be presented to our national audience as part of the *Breast Cancer Update* audio series.

We are also launching a new web-based interface to support this effort — DesignATrial.com. The site will allow for an ongoing, international interchange on new clinical trial ideas.

We ask participants in "Design A Trial" to stretch

their imaginations and put funding practicalities aside. You have been given a monstrous grant to

do your trial the way it needs to be done. Tell us all about it.

FIRST ANNUAL DESIGN A CLINICAL TRIAL CHALLENGE

Submit your innovative ideas for future breast cancer clinical trials to DesignATrial.com or visit our clinical trials education booth in Hall C at San Antonio.

Tell us briefly what you want to study and why. Our panel of esteemed clinical researchers will evaluate all the entries and vote on the best. The authors of the five most interesting trial designs as determined by our panel will be invited to present

and discuss their ideas during a special educational roundtable and audio recording session in Miami, Florida in February 2007.

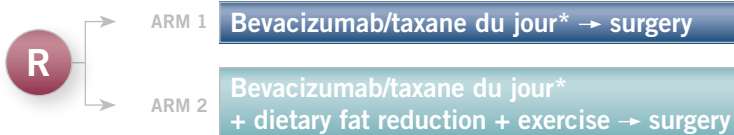
All entries must be received by December 31, 2006 and winners will be notified by January 22, 2007. So go ahead, think outside of the box — then think outside of that box and let us know what you come up with.

Here's my entry:

TNT — Triple Negative Trial

Neoadjuvant therapy of basaloid breast cancer

TRIAL DESIGN



KEY FACTS

Eligibility

- ER-negative, PR-negative, HER2-negative invasive breast cancer greater than 2 cm

Primary Endpoint

- Pathologic complete response

* Physician's choice of 4 months of paclitaxel, nanoparticle albumin-bound paclitaxel or docetaxel

Tissue Correlative Study

Serum and tissue samples will be obtained before treatment and at surgery, along with dynamic flow studies of the breast

Projected Accrual (1 year): 1,500 patients

RATIONALE

Seemed like a good idea at the time. No, seriously, the WINS study cannot be ignored. Why did women with ER-negative tumors have fewer relapses with dietary fat reduction? Subset mischievousness? I don't think so.

Also, how does one explain the repeated signals about exercise and relapse in breast and colon cancer? Is it all about insulin, or is it more complicated than that?

Whatever the mysterious effects of these interventions are, would there be synergy with maybe our best known systemic therapy for triple-negative tumors?

My personal choice for a taxane would be *nab* as opposed to the other available taxanes. I don't want premedications messing up my perioperative cocktail, and steroids might make it difficult for patients to control their food intake. Postop-

erative therapy, if any, will be the physician's choice. All patients will also be eligible to receive postop exercise and nutritional interventions. Let me know what you think of this design and

submit your ideas at DesignATrial.com. Maybe I'll try to present my TNT trial at the NCI meeting on preoperative therapy next March (<http://ctep.cancer.gov/bcmeeting>).

One Patient's Perspective on "Design A Trial"

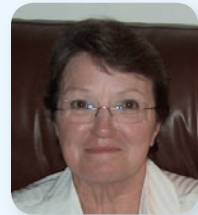
Editor: *As this program was about to go to print, I received the following email from Mrs Sandra Martinez, who for the last nine years has been the lead transcriptionist for our CME group. In 2004, Mrs Martinez was diagnosed with breast cancer, an experience that further increased her already intense interest in oncology.*

Hi Neil,

Several of the recent interviews have discussed the new "Design A Trial" project, and while I certainly don't presume to know about the intricacies of chemotherapy and targeted treatment, I think that the patient can be kind of forgotten in trials, and sometimes we seem to get lost in the percentages and statistics.

As someone who has been typing about various types of cancer for a good number of years, I have often wondered whether some factors could be incorporated into trials that might be more relevant to patients. Has there ever been a quality-of-life trial meta-analysis of what helped patients cope and what didn't? Maybe some trials should incorporate along with the regular therapeutic arms an antidepressant arm versus no antidepressant arm, and then at varying doses.

Life for a cancer patient isn't just about keeping breathing, it's also about enjoying every breath you take. Depression — usually present whether recognized or not — plays a huge role in this process. I also wonder about doing a trial that evaluates laughter therapy. No, I don't know how to accomplish all this; I just know what's important to me as a patient and what has helped me cope with some of the many challenges a cancer patient faces. Just my thought for the day.



Sandra Martinez

— Sandra

EDUCATE

If you are already a believer in the importance of clinical trials, we want to make it easier for you to spread the word, and to do this we have produced a PowerPoint slide presentation and Speaker's Kit based on the content of this monograph, which is available at our education exhibit at the conference and online at BreastCancerUpdate.com/ClinicalTrials. We encourage you to take home a complimentary

copy of this program and incorporate the slides into your lectures and presentations.

The May 16th message is out there. We have the technology. Let's get this thing done.

— Neil Love, MD
NLove@ResearchToPractice.net

Special thanks to SABCS co-director Dr Kent Osborne for working with us to develop this initiative and for reviewing the enclosed education materials.

The adjuvant trastuzumab spectacle has another important component to consider in what could become a new oncology research model — the dissemination of important trial results into clinical practice. In addition to dramatically enhancing the molecular targeted research model, the adjuvant trastuzumab trial findings

are also testimony to the efficiency of the current translation of trial results to patient care.

The following is a graphic history of how medical oncology practice changed almost instantaneously following the landmark 2005 ASCO “education session” that featured several presentations on this important therapeutic advancement.

PRE-ASCO 2005 PATTERNS OF CARE

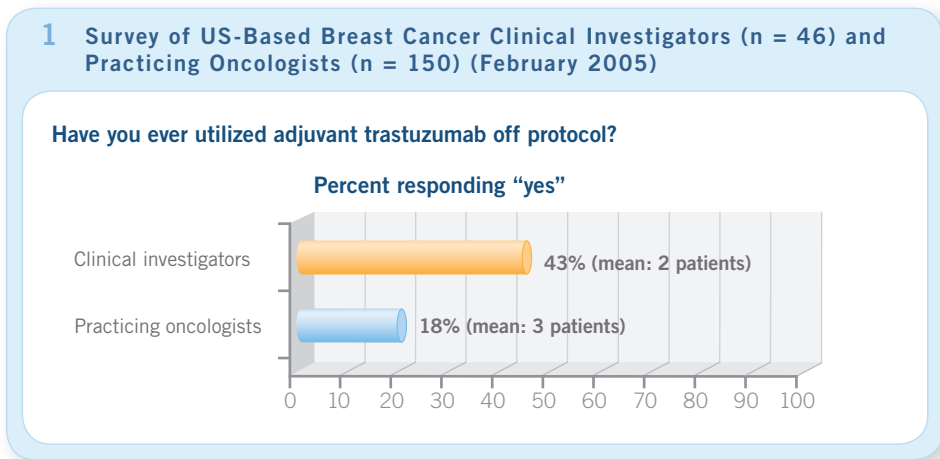
From the launch of the adjuvant trastuzumab trials in 2000 until the first release of the data in 2005, clinical investigators — with few exceptions — repeatedly emphasized that the use of trastuzumab as adjuvant therapy *outside* a protocol setting was not a good idea.

Frequent references were made to the stem-cell debacle as proof that the early adoption of unproven therapies is unwise and potentially dangerous.

One notable exception along the way was Dennis Slamon, who, during a 2002 interview for our *Breast Cancer Update* audio series, unflinchingly presented a woman with a HER2-positive, node-negative tumor who was not eligible for a clinical trial and chose to receive adjuvant TCH based on Dr Slamon’s recommendation.

However, with few exceptions, community-based oncologists seemed to heed the words of the majority of their research-focused counterparts, and prior to May 2005 both groups rarely used adjuvant trastuzumab outside of a clinical trial (Figure 1).

Of interest, our CME group conducted several anonymous polls during this time asking oncologists, “If you or a loved one were diagnosed with HER2-positive breast cancer with 10 positive nodes, would you want to receive adjuvant trastuzumab?” Many said, “Yes,” and one wonders whether we should reconsider the current mandate to practice strict evidence-based medicine when we are contemplating the use of promising therapies with modest toxicities.



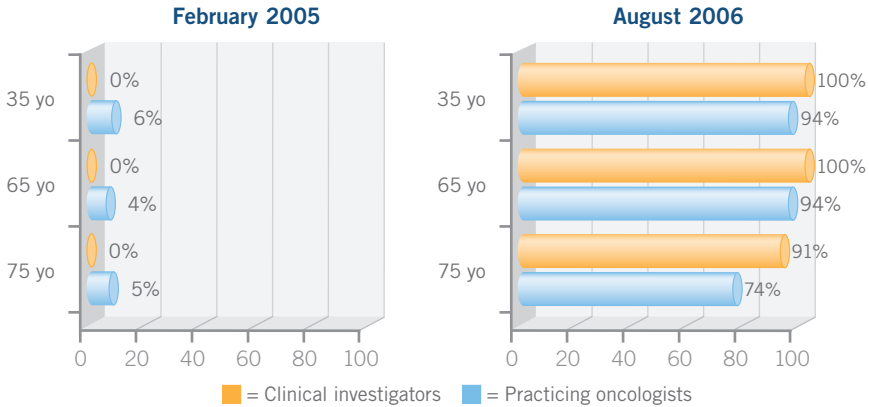
PATTERNS OF CARE AFTER THE 2005 ASCO MEETING

In February 2005, when we presented cases of women with ER-negative, HER2-positive tumors and three positive nodes, none of the clinical investigators and only a small percentage of

practicing oncologists would recommend trastuzumab (Figure 2a — February). Just a couple months after ASCO 2005, practice patterns had already changed dramatically. When we presented

2a Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150)

Case: A patient with a 1.2-centimeter, ER-negative, HER2-positive, Grade II tumor with three positive nodes. Would you use adjuvant trastuzumab off protocol for this patient? (Percent responding “yes”)



the same cases in August 2005, nearly 100 percent of clinical investigators and more than 90 percent of practicing oncologists would recommend trastuzumab for most patients (Figure 2a — August). Our August survey indicated that the majority of clinical investigators and practicing oncologists were using trastuzumab for patients with HER2-positive tumors who met the entry criteria for these trials (Figures 2b, 2c).

The accurate assessment of the HER2 status of a patient's tumor is even more critical now than pre-2005 ASCO. Currently, there is a divergence of opinion as to what constitutes HER2 positivity (Figure 3), and great concerns continue to exist regarding quality control in HER2 testing (and of course ER testing).

However, poor pathology quality control can lead to patients receiving inappropriate and ineffective therapy. This is a shameful travesty. The recent efforts by ASCO and the NCCN to put some pressure on the pathology community are just the beginning. This situation needs to be fixed yesterday.

Focusing on the specific utilization of adjuvant trastuzumab in practice, a clear trend has emerged. Clinicians, as they so often do in medical oncology, are most commonly following the data and mimicking the two US-based trials by integrating trastuzumab with a taxane after an anthracycline regimen. It is interesting to note that many physicians are using dose-dense

AC → paclitaxel/trastuzumab, although none of the major reported randomized trials utilized this chemotherapy backbone (Figure 4).

The adaptation of the dose-dense platform for patients receiving trastuzumab is no surprise given that for the past several years, our Patterns of Care studies have demonstrated that this regimen is by far the most common adjuvant chemotherapy used for patients with node-positive disease.

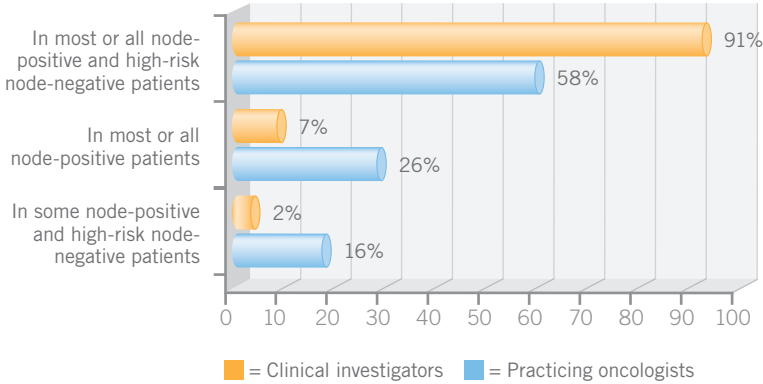
In keeping with the theme of “following the data,” virtually all clinical investigators and most practicing oncologists are prescribing adjuvant trastuzumab for the trial standard of one year and are also following the recommendations of Edith Perez and others by starting trastuzumab concurrently with taxane chemotherapy rather than using the agents sequentially.

From day one, there have been many questions and much uncertainty about the use of adjuvant trastuzumab without chemotherapy, either alone (Figure 5) or with endocrine therapy for patients with ER-positive tumors.

Although this treatment approach may be appealing in some unusual situations (eg, octogenarians in suboptimal general health), the 50 percent relative reduction in relapse rate with trastuzumab/chemotherapy has most docs again trying to stick with the data and considering perhaps even a single-agent taxane along with the anti-HER2 agent for frail and elderly patients.

2b Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150) (August 2005)

Have you used (or do you plan to use) trastuzumab in the adjuvant setting?

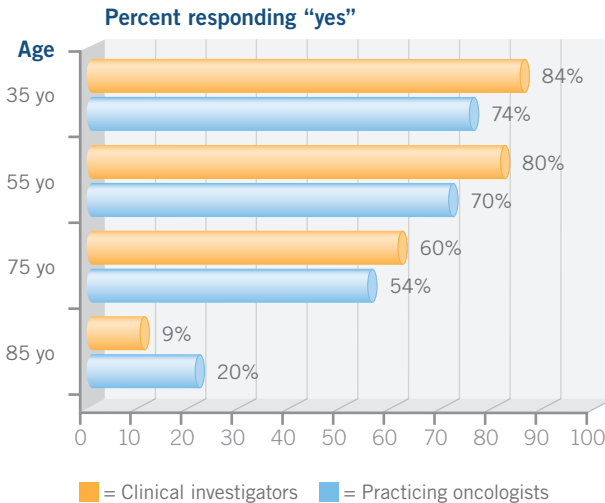


Average number of patients treated with adjuvant trastuzumab:
 Clinical investigators = 27; practicing oncologists = 23

2c Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150) (August 2005)

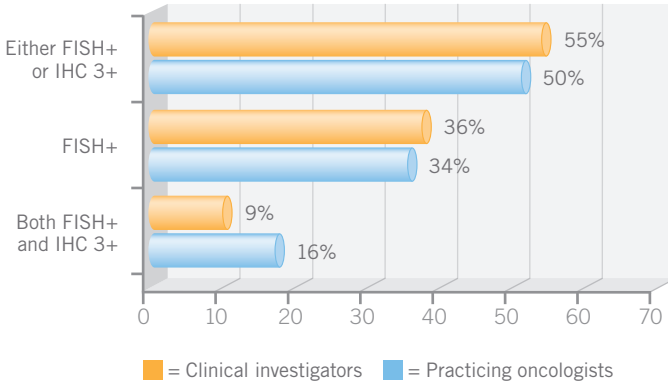
Case: A patient with a 1.2-centimeter, ER-negative, HER2-positive, Grade II tumor with no positive nodes.

Would you use adjuvant trastuzumab off protocol for this patient?



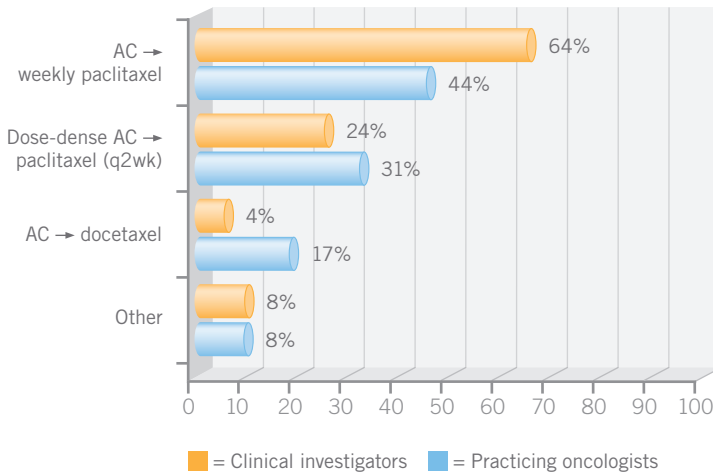
3 Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150) (August 2005)

What documentation of HER2 positivity do you/will you require to use adjuvant trastuzumab?



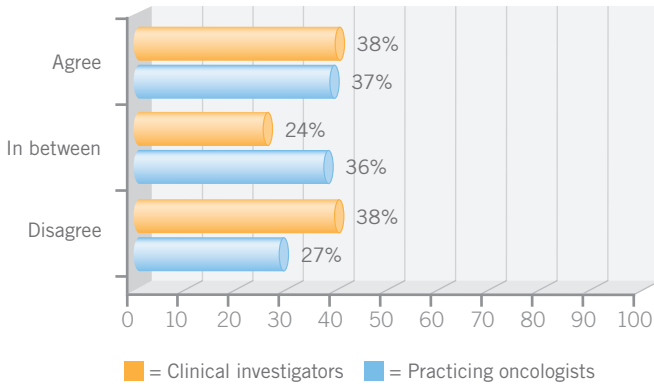
4 Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150) (August 2005)

When using adjuvant trastuzumab for breast cancer patients, what adjuvant chemotherapy regimen do you generally use?



5 Survey of US-Based Breast Cancer Clinical Investigators (n = 46) and Practicing Oncologists (n = 150) (August 2005)

Trastuzumab monotherapy is a reasonable off-protocol adjuvant treatment option for breast cancer patients who are unable to receive chemotherapy.



MAY 2005 AS A MODEL OF RESEARCH TO ONCOLOGIC PRACTICE

It was mighty interesting to have been in the middle of this seismic shift in oncology practice. As with all ASCO meetings, I had arranged to conduct interviews in Orlando with a number of breast cancer clinical investigators at the conference.

As the principal investigator of NSABP-B-31, Ed Romond from the University of Kentucky was at the top of our list to interview. I had the highly interesting opportunity to sit down with Ed immediately after the education session in which he presented the initial combined NSABP/NCCTG data.

As one might expect, Dr Romond was ebullient and filled with energy and optimism. However, he began our conversation not by plowing through the data but by telling me what was going through his mind as he stood before the audience in Orlando poised to unleash the research equivalent of a Category 5 data storm.

Ed's thoughts were with one of the patients he evaluated for participation in NSABP-B-31 several years ago. This young, single mother of an 11-year-old son had a HER2-positive tumor and 25 positive lymph nodes. She desperately wanted to enter the study but lived two hours from Lexington and had no means of transportation to take her to and from the frequent clinic

visits the trial required.

Ed told me with considerable emotion that to solve this problem, the patient's father — at great sacrifice — purchased a car so that she could participate in the study. This woman was randomly assigned to the trastuzumab arm and currently remains free of cancer three years later.

I imagine that many of the investigators and practicing oncologists who enrolled patients on these groundbreaking trials have similar stories to tell, and it is no wonder that a sense of intense, almost overwhelming emotion consumed the meeting hall that day in Orlando, as the enormous human implications of these data became obvious to us all.

The morning after the session, I scooped up George Sledge in the lobby of the Omni hotel at the ungodly surgical hour of 6:00 AM. It was the only time George had in his schedule for an interview, and I was deeply grateful that he met with me.

His words and Ed's would soon be heard by thousands of oncologists and undoubtedly guided a great deal of clinical practice that summer.

Those interviews, and other CME outlets and meetings, helped get the word out quickly, and surely played a role in changing clinical practice.

In my mind, this is a triumph of the interface between the clinical trials system and current methods for the communication of oncology information and perspectives.

It's comforting to consider the life cycle that started with a series of well-designed and well-executed clinical trials and ended with people

like Ed's patient perhaps avoiding relapse and death as a result. We need to repeat this cycle until we get this thing done.

Somewhere in the hills of Kentucky, this woman, with her son next to her, glides along in a loving vehicle that brought them to a place none of us could have imagined a few years ago. ■

SELECT PUBLICATIONS

Baselga J et al. **Adjuvant trastuzumab: A milestone in the treatment of HER-2-positive early breast cancer.** *Oncologist* 2006;11(Suppl 1):4-12. [Abstract](#)

Carlson RW; NCCN HER2 Testing in Breast Cancer Task Force. **HER2 testing in breast cancer: NCCN Task Force report and recommendations.** *J Natl Compr Canc Netw* 2006;4(Suppl 3):1-22. [Abstract](#)

Geyer CE Jr et al. **Update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC) → paclitaxel (T) vs AC → T with trastuzumab (H).** *Proc ASCO* 2006;[Abstract 581](#).

Gonzalez-Angulo AM et al. **Adjuvant therapy with trastuzumab for HER-2/neu-positive breast cancer.** *Oncologist* 2006;11(8):857-67. [Abstract](#)

Hurley J et al. **Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer.** *J Clin Oncol* 2006;24(12):1831-8. [Abstract](#)

Joensuu H et al. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. [Abstract](#)

Kelly H et al. **Response and cardiac toxicity of trastuzumab given in conjunction with weekly paclitaxel after doxorubicin/cyclophosphamide.** *Clin Breast Cancer* 2006;7(3):237-43. [Abstract](#)

Love N; Research To Practice. **Management of breast cancer in the adjuvant and metastatic settings.** *Patterns of Care in Medical Oncology* 2005;2(1).

Love N; Research To Practice. **Management of breast cancer in the adjuvant and metastatic settings.** *Patterns of Care in Medical Oncology* 2005;2(2).

Mehra R, Burtness B. **Antibody therapy for early-stage breast cancer: Trastuzumab adjuvant and neoadjuvant trials.** *Expert Opin Biol Ther* 2006;6(9):951-62. [Abstract](#)

Perez EA et al. **HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial.** *J Clin Oncol* 2006;24(19):3032-8. [Abstract](#)

Persons DL et al. **HER-2 fluorescence in situ hybridization: Results from the survey program of the College of American Pathologists.** *Arch Pathol Lab Med* 2006;130(3):325-31. [Abstract](#)

Piccart-Gebhart MJ. **Adjuvant trastuzumab therapy for HER2-overexpressing breast cancer: What we know and what we still need to learn.** *Eur J Cancer* 2006;42(12):1715-9. [Abstract](#)

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. [Abstract](#)

Press MF et al. **Diagnostic evaluation of HER-2 as a molecular target: An assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials.** *Clin Cancer Res* 2005;11(18):6598-607. [Abstract](#)

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. [Abstract](#)

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** San Antonio Breast Cancer Symposium 2005;[Abstract 1](#).

Smith KL et al. **Cardiac dysfunction associated with trastuzumab.** *Expert Opin Drug Saf* 2006;5(5):619-29. [Abstract](#)

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. [Abstract](#)

Tsuda H. **HER-2 (c-erbB-2) test update: Present status and problems.** *Breast Cancer* 2006;13(3):236-48. [Abstract](#)

Neoadjuvant Therapy

1. What is the optimal aromatase inhibitor for neoadjuvant therapy? **ACOSOG-Z1031**
2. What is the optimal neoadjuvant therapy for women with HER2-negative breast cancer? **NSABP-B-40**

Radiation Therapy

3. Does partial breast irradiation (PBI) provide equivalent local tumor control compared to whole breast irradiation (WBI) following lumpectomy? **NSABP-B-39**

Adjuvant Endocrine Therapy

4. What is the optimal adjuvant endocrine therapy for postmenopausal women with DCIS? **IBIS-II (DCIS)/NSABP-B-35**
5. What is the optimal duration of adjuvant aromatase inhibitor therapy? **NSABP-B-42**
6. Which is the safest and most efficacious aromatase inhibitor as up-front adjuvant therapy for postmenopausal women? **CFEM345D2411**
7. What is the optimal adjuvant endocrine therapy for premenopausal patients? **SOFT/TEXT/PERCHE**

Adjuvant Chemotherapy

8. Which adjuvant bisphosphonate is most effective at preventing metastases? **SWOG-S0307**
9. What is the utility of adjuvant chemotherapy for patients with intermediate recurrence scores of the *Oncotype DX™* assay? **TAILORx**
10. Is oral, single-agent capecitabine as effective as standard adjuvant AC or CMF in older patients? **CALGB-49907**
11. What is the optimal chemotherapy regimen for patients with lower-risk node-positive or node-negative disease? **CALGB-40101/NSABP-B-36**
12. What is the optimal adjuvant chemotherapy regimen for patients with node-positive or higher-risk node-negative disease? **SWOG-S0221**
13. What is the optimal adjuvant chemotherapy regimen for patients with node-positive disease? **NSABP-B-38**
14. Is it safe to combine bevacizumab with dose-dense adjuvant chemotherapy? **ECOG-E2104**
15. Is bevacizumab a safe and effective treatment for residual disease after preoperative chemotherapy? **NCT00121134**

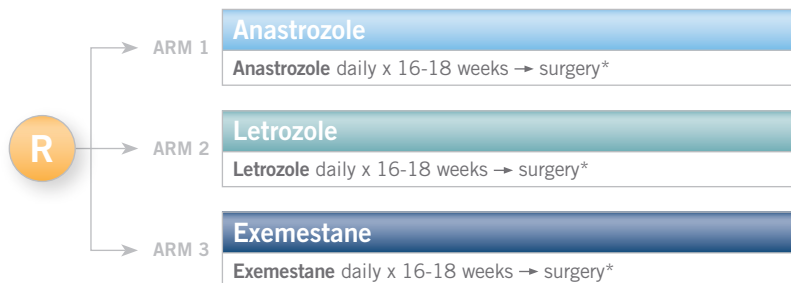
Metastatic Disease

16. What is the optimal endocrine therapy for postmenopausal patients with metastases and disease progression on a nonsteroidal aromatase inhibitor? **SoFEA/SWOG-S0226/FACT**
17. What is the optimal dosing of fulvestrant for postmenopausal patients? **CONFIRM**
18. Does lapatinib improve outcomes when combined with trastuzumab in patients with HER2-positive metastatic disease? **EGF104383/EGF104900**
19. Does bevacizumab add benefit to endocrine therapy for metastatic disease? **CALGB-40503 (proposed)**
20. Can HER2 and ER cross-talk be therapeutically exploited by combining fulvestrant and trastuzumab? **UCLA-0502057-01**
21. What is the benefit of adding bevacizumab to chemotherapy as first- and second-line therapy? **RIBBON 1/RIBBON 2**

ACOSOG-Z1031

A Phase III neoadjuvant trial of anastrozole versus letrozole versus exemestane

TRIAL DESIGN



* Partial or radical mastectomy or lumpectomy with or without lymph node dissection

KEY FACTS

Select Eligibility Criteria

- Postmenopausal
- T2-T4c breast cancer
- ER-positive with Allred score of 6, 7 or 8
- Palpable tumor, two centimeters by caliper
- No inflammatory breast cancer
- No distant metastasis (M1)

Primary Objective

- Selection of anastrozole, letrozole or exemestane as the aromatase inhibitor in a future study comparing neoadjuvant aromatase inhibitor treatment with neoadjuvant chemotherapy

Secondary Objectives

- Cell cycle response
- Predictive biomarkers

- Rates of improvement in surgical outcome, radiological response rates, safety, tumor pathologic size, pathologic complete response, metastatic lymph node involvement in patients with lymph node dissection following neoadjuvant treatment, five-year local recurrence rate

Target Accrual: 375

Current Accrual: 22 (10/02/2006)

Date Activated: January 9, 2006

Study Contacts

American College of Surgeons Oncology Group
Matthew Ellis, MD, PhD, FRCP, Protocol Chair
John Olson, MD, PhD, Protocol Co-Chair

SOURCES: ACOSOG-Z1031 Protocol vA4; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► We're significantly more likely to be successful performing breast-conserving surgery after neoadjuvant endocrine therapy than chemotherapy. One reason for this is that approximately 20

to 30 percent of patients who respond well to neoadjuvant chemotherapy are left with multiple islands of tumor scattered throughout an area of the breast that corresponds to the size of the

original tumor, whereas the pattern following neoadjuvant endocrine therapy is that the tumor shrinks and implodes.

The number of patients receiving neoadjuvant endocrine therapy has increased significantly, and many oncologists who have tried this approach and found that it worked have adopted this strategy.

I believe more physicians should be using this because it's effective at downstaging some large tumors, making inoperable tumors operable.

When we're selective and treat only patients with ER-rich tumors, meaning Allred scores 6, 7 and 8, the number of patients who progress or actually fail to respond is small.

We have also learned that we can treat patients longer than three or four months with neoadjuvant therapy and see continued response.

We've treated patients for up to a year and found that the number of patients with a complete response continues to rise the longer we treat them.

If the tumor is shrinking but still is not small enough for breast-conserving surgery at three or four months, continuing therapy will give added benefit, and eventually, most of these tumors will become small enough for breast conservation. ■

— J Michael Dixon, MD

► I believe it was a mistake to evaluate chemotherapy rather than endocrine therapy in some of the earlier neoadjuvant studies.

The perioperative phase is critical and although no evidence indicates that preoperative chemotherapy improves survival, that's nonspecific treatment, and it doesn't mean that neoadjuvant endocrine therapies will fail.

I view neoadjuvant endocrine treatment as a biological response modifier, and I believe using the aromatase inhibitors up front might have a greater impact on long-term outcome. ■

— Michael Baum, MD, ChM

SUPPORTING PROTOCOL INFORMATION

Background Information

The long-term aim of the ACOSOG neoadjuvant endocrine therapy research program is to conduct a practice-setting randomized trial of neoadjuvant chemotherapy versus neoadjuvant endocrine therapy to establish neoadjuvant endocrine therapy as a routine treatment option. The objective of Z1031 is to resolve questions regarding protocol design.

The first question concerns the choice of aromatase inhibitor. The primary objective of this initial study is to compare the activity of anastrozole, letrozole and exemestane as neoadjuvant treatment.

A selection design (rather than a superiority design) has been adopted because the aim is simply to determine whether a particular aromatase inhibitor should be chosen for the comparison with chemotherapy.

If no major differences are found, an open-label choice of any of the three third-generation aromatase inhibitors may be adopted.

A second objective is to define a patient group, based on predictive biomarker research, in which the aromatase inhibitor response rate is sufficiently high to be potentially more effective than chemotherapy.

This would allow the direct comparison with

chemotherapy to be based on a superiority design in favor of aromatase inhibitor treatment.

A third objective is to delineate the clinical and biomarker endpoints that will be used to rigorously judge the effectiveness of neoadjuvant endocrine therapy.

The use of neoadjuvant endocrine therapy in place of neoadjuvant chemotherapy can be justified on the basis that the patients in question (postmenopausal women with estrogen receptor-positive tumors) are receiving a form of systemic treatment that, in the adjuvant setting, is at least twice as effective as chemotherapy in providing long-term protection from relapse and death from breast cancer.

Correlative Science Program

The central theme of the primary tumor-based correlative science study is to develop an aromatase inhibitor response signature that can be translated into a widely applicable test that can be used to identify patients with a high chance of responding to aromatase inhibitor therapy in either the adjuvant or neoadjuvant setting.

Since the correlative science analysis will be conducted across the three arms of the trial, the response signature that is developed will be broadly applicable and not agent specific.

NSABP-B-40

A Phase III randomized trial of six neoadjuvant regimens in patients with palpable and operable HER2-negative breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Palpable breast mass ≥ 2.0 cm
- HER2-negative

Stratification

- Clinical tumor size (2.0-4.0 cm, >4.0 cm)
- Clinical nodal status (negative, positive)
- Hormone receptor status (ER-positive and/or PR-positive, ER-negative and PR-negative)
- Age (<50 , ≥ 50)

Other Therapy

- Patients with ER-positive and/or PR-positive disease receive a minimum of five years of hormonal therapy

- Postoperative radiation therapy administered at the physician's discretion

Primary Endpoint

- Pathologic complete response (pCR) rate in the breast

Secondary Endpoints

- pCR rate in axillary nodes, clinical overall response rate (cOR), clinical complete response rate (cCR), disease-free survival, surgical complication rates, toxicity, adverse effects on cardiac function

Proposed Sample Size: 1,200

Open to Enrollment: 11/20/06

SOURCES: NSABP Group Meeting, April 2006; nsabp.pitt.edu.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► The novelty of NSABP-B-40 is that we're using pCR as an endpoint with an emphasis on developing a molecular taxonomy to determine whether or not we can characterize patients who obtain a pCR as a surrogate marker to measure outcome. Disease-free and overall survival are not primary endpoints for NSABP-B-40. We view it as a new mechanism to test promising agents in the neoadjuvant setting, and we think it is an appropriate direction to pursue, particularly with the number of agents that are available and the limited resources, both from a support standpoint and a population standpoint. ■

— Norman Wolmark, MD

► NSABP-B-40 was originally going to be a three-arm study evaluating sequential AC followed by either docetaxel alone, docetaxel with capecitabine or docetaxel with gemcitabine. We were about to open the trial but decided to modify it to incorporate bevacizumab. With that, we reconfigured the study to move the taxane ahead of the AC, which is the reversal of the usual order.

Our thinking was twofold. One, the data for bevacizumab in breast cancer were with a taxane. Hence, we wanted to administer the two together as much as possible. Then, there was also concern about the possibility of increased cardiac toxicity for the anthracyclines with bevacizumab. More and more, it's looking as if that probably isn't going to be a concern. ■

— Charles E Geyer Jr, MD

► The NSABP-B-40 trial has evolved over a very long period of time since we completed accrual to B-27. From the beginning, we wanted to evaluate the impact of adding a biologic response modifier. We studied a lot of them over the period of years that this has been developed, and each one we evaluated did not pan out to have the activity that we thought indicated that it would be useful in this setting.

— Harry D Bear, MD, PhD

Certainly, bevacizumab has come along recently as a promising drug not only in the metastatic setting but also in the locally advanced neoadjuvant setting, in a study by Sandra Swain's group at the NCI.

We are now poised to do a number of things with B-40. One is to examine different docetaxel doublets combined with capecitabine or gemcitabine as potential ways to increase response and improve patient outcomes and then to add bevacizumab to the chemotherapy, which may not only be beneficial but potentially synergistic with the chemotherapy.

We will be administering the docetaxel or docetaxel doublets first, which is different from our previous design. This is mainly to take advantage of the documented synergy between a taxane and bevacizumab and to allow us to stop the bevacizumab before surgery so we don't run into surgical complications as a result of angiogenesis inhibition. It allows a washout period.

One of the most important outcomes of the study involves correlative science. We will be requiring the submission of four cores of tissue prior to the randomization. Two cores will be put in RNAlater® to preserve the RNA, so we can do gene-expression profiling. Another core will be put in a fixative for later use for other molecular analyses like Genomic Health's assay, and a fourth core will be put in a medium for assessment by a chemosensitivity assay.

One of the exciting things about this study is the attempt to further understand the mechanism of action of bevacizumab. We have evidence that macroscopic tumor shrinkage may be synergistic between bevacizumab and chemotherapy, and the NCI showed nicely that cancer cells express VEGF receptor and the phosphorylation of that receptor is dramatically downregulated in patients who respond to bevacizumab, so there may be a significant effect on the tumor cells directly and on the tumor's blood supply. ■

SUPPORTING PROTOCOL INFORMATION

Correlative Science Program

Pathology specimens will be collected and used to identify gene expression profiles that can predict pCR and to test a chemosensitivity assay as a predictor of pCR. Submission of core needle biopsy specimens is a pre-entry requirement for participation in B-40. Tumor blocks from any

gross residual disease at the time of surgery are also required for all patients in B-40.

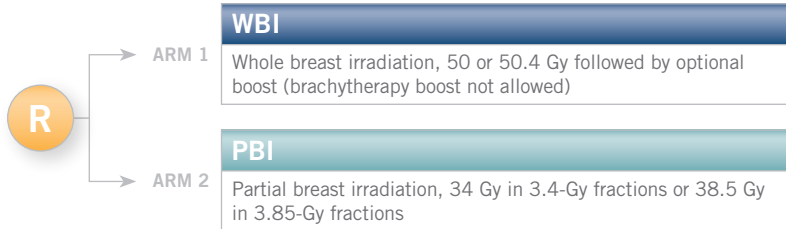
If no gross residual disease is found at surgery, the submission is required of two unstained slides from each of the blocks from the area of the breast where the tumor had been.

Does partial breast irradiation (PBI) provide equivalent local tumor control compared to whole breast irradiation (WBI) following lumpectomy?

NSABP-B-39; RTOG-0413

A randomized Phase III study of conventional whole breast irradiation versus partial breast irradiation for early-stage breast cancer

TRIAL DESIGN



KEY FACTS

Partial Breast Irradiation

Radiation therapy administered to tissue surrounding lumpectomy cavity only. The PBI techniques utilized will be at the physician's discretion and will be based on technical considerations, radiation oncology facility credentialing and patient preference.

Select Eligibility Criteria

- Stage 0, I or II invasive adenocarcinoma. If Stage II, tumor must be ≤ 3 centimeters
- Less than four positive axillary nodes
- Surgery must have been lumpectomy with free margins (re-excision permitted)
- Target cavity/whole breast reference volume must be ≤ 30 percent on postoperative/pre-randomization CT scan
- Gross disease must be unifocal. Microscopic multifocality allowed if total pathologic tumor size is ≤ 3 centimeters
- Axillary staging is required for invasive carcinoma

Primary Endpoint

- Time to in-breast tumor recurrence

Secondary Endpoints

- Survival, recurrence-free survival, distant disease-free survival, quality of life, toxicities

Primary Hypothesis

This study will be designed to (1) establish the equivalency in local control and overall survival of PBI to WBI, (2) establish the equivalency in cosmetic outcome between the two treatment approaches and (3) analyze potential differences in fatigue, treatment-related symptoms and convenience of care among patients undergoing PBI versus WBI.

Target Accrual: 3,000 over 2.5 years

Current Accrual: 2,031 (10/02/06)

Date Activated: March 21, 2005

Study Contacts

National Surgical Adjuvant Breast and Bowel Project

Frank Vicini, MD, FACR, Protocol Chair

Radiation Therapy Oncology Group

Julia White, MD, Protocol Chair

Southwest Oncology Group

Lori Pierce, MD, Protocol Chair

SOURCES: NSABP-B-39 Protocol, March 2006; nsabp.pitt.edu.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► To understand the rationale for this Phase III trial, you have to understand that when we began using partial breast irradiation, we selected patients carefully — patients with small tumors, clear margins and negative lymph nodes. We

were trying to determine whether this technique was as efficacious as whole breast irradiation, but we selected only patients at low risk and, indeed, the five- and 10-year results with these low-risk cases have been good.

However, with the NSABP-B-39 trial, the eligibility criteria have been loosened significantly. We are treating patients with up to three positive lymph nodes and tumors of up to three centimeters. We're including multiple types of histologies, not just infiltrating ductal carcinomas. The B-39 trial has been designed to test whether partial breast irradiation could be used for patients at a slightly higher risk or whether it should be restricted to patients at a lower risk.

The three partial breast irradiation techniques used in the trial are brachytherapy with the traditional multiple needles, the MammoSite™ balloon catheter and 3-D conformal external beam radiation therapy. If a patient is interested in participating in the trial, we first do a prerandomization CT scan. The radiation oncologist, with assistance from the surgeon, will examine the lumpectomy cavity on the CT scan to determine whether a patient is a candidate for partial breast irradiation and then, specifically, which partial breast irradiation technique that patient is qualified for from a technical standpoint.

If the patient qualifies for one of the techniques, we let her know. If she agrees to that technique, the patient is then randomly assigned to either whole breast irradiation therapy or that particular partial breast irradiation therapy. If the patient is a candidate for all three partial breast irradiation techniques, then she tells us which one

she wants and the randomization is between whole breast irradiation and the technique she's chosen. ■

— Frank A Vicini, MD

► In our population-based study utilizing SEER registry data to evaluate patient decision-making in the selection of mastectomy versus breast-conserving surgery, we observed significant concerns about radiation therapy, which were due to a mixture of fears of radiation toxicity and concerns about the six weeks of conventional treatment. Partial breast irradiation has the opportunity to increase breast conservation rates particularly for working women, lower-income women and women in rural areas.

The results of the joint NSABP/RTOG trial are going to be important because even though the rationale behind partial breast irradiation is sound, most local recurrences occur in the area of the primary tumor, and whole breast irradiation does not prevent the long-term development of second primary cancers. We have to see whether or not local control is as good as with whole breast irradiation, particularly with cosmetic outcome, and whether shorter-term treatments at higher doses result in greater rates of fibrosis, retraction and fat necrosis. ■

— Monica Morrow, MD

SUPPORTING PROTOCOL INFORMATION

Background Information

Can an acceptable outcome be achieved with radiotherapy (RT) delivered only to the region of the tumor bed? If this were the case, radiation therapy could be delivered in 1 to 2 weeks, thus significantly shortening treatment time and potentially reducing health care costs. A shortened treatment schedule would decrease the burden of care for patients undergoing breast conserving therapy (BCT), thus making available the conservation option for more women. By reducing the length of time required to deliver RT, the logistical problems associated with integrating local and systemic therapies would also be eliminated.

Additionally, toxicity to adjacent normal structures (ie, heart, underlying chest wall, contralateral breast) should be reduced significantly by decreasing the volume of irradiated tissue.

Several recent meta-analyses on the use of RT for breast cancer patients clearly document a reduction in cancer-specific mortality during

the first 5-10 years after treatment that is partially offset by late effects of radiation on adjacent tissues. Since it remains uncertain if the additional volume of normal tissue that is irradiated (in order to encompass the entire breast for presumed occult disease) provides any additional benefit in reducing breast cancer recurrence, the potential detrimental effects of this additional RT would be eliminated.

Correlative Science Program

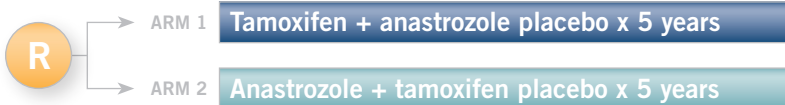
The aim of the pathology and correlative science for this trial is to identify potential predictors of selective advantage for WBI versus PBI. There will be two important aspects for correlative science studies: (1) predictors of multicentricity and local recurrence after lumpectomy without radiotherapy will have significant bearing on outcome of patients in the PBI arm, and (2) markers of radiosensitivity/resistance should be examined since, if the tumor cells are resistant to radiotherapy, the local recurrence rate will not be influenced by the field of radiation.

IBIS-II (DCIS) and NSABP-B-35 (closed to accrual)

Tamoxifen versus anastrozole in postmenopausal women with ductal carcinoma in situ (DCIS)

TRIAL DESIGNS

IBIS-II



KEY FACTS

Select Eligibility Criteria

- Postmenopausal between the ages of 40-70
- Tumor confined to the breast and axillary nodes
- ER-positive and/or PR-positive (>5%)
- Baseline bone mineral density scan within the last two years
- Locally excised DCIS diagnosed within the last six months

Primary Endpoint

- Development of invasive or noninvasive (new or recurrent DCIS) breast cancer

Secondary Endpoints

- Efficacy according to the receptor status of the primary or recurrent cancer
- Rate of recurrence or new contralateral tumors after treatment cessation with tamoxifen or anastrozole

- Breast cancer mortality
- Drug effects on other cancers, cardiovascular disease, fracture rates and nonbreast cancer deaths
- Tolerability and acceptability of side effects

Target Accrual: 4,000 within 4 years

Date Activated: May 2003

Study Contacts

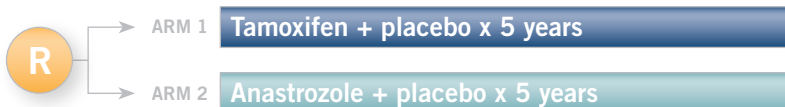
Cancer Research UK at Imperial College School of Medicine — London
 Jack Cuzick, PhD, Study Coordinator
 International Breast Cancer Study Group
 Katharina Buser, MD, Protocol Chair

SOURCES: CRUK-IBIS-II (DCIS) Protocol, July 2005; ibis-trials.org.

NSABP-B-35 (closed)

Closed to accrual 6/15/2006; N = 3,000+

A clinical trial comparing anastrozole to tamoxifen in postmenopausal patients with ER-positive or PR-positive DCIS undergoing lumpectomy with radiation therapy



SOURCES: NCI Physician Data Query, October 2006; cancer.gov.

IBIS-II prevention

A randomized prevention study of anastrozole in postmenopausal women at increased risk of breast cancer



KEY FACTS

Select Eligibility Criteria

Meets at least one of the relative risk factors based on age as follows:

- **45 to 70 years of age**
 - First-degree relative with breast cancer at ≤ 50 or with bilateral breast cancer
 - Two or more first- or second-degree relatives with breast or ovarian cancer
 - Nulliparous (or first birth at ≥ 30) and a first-degree relative with breast cancer
 - Benign biopsy with proliferative disease and a first-degree relative who developed breast cancer
 - Mammographic opacity covering at least 50 percent of the breast in the absence of HRT within the past three months
- **60 to 70 years of age**
 - First-degree relative with breast cancer at any age
 - Age at menopause ≥ 55
 - Nulliparous (or first birth at ≥ 30)
- **40 to 44 years of age**
 - Two or more first- or second-degree relatives who developed breast or ovarian cancer at ≤ 50
 - First-degree relative with bilateral breast cancer with first breast cancer at ≤ 50
 - Nulliparous (or first birth at > 30) and a first-degree relative with breast cancer at ≤ 40
 - Benign biopsy with proliferative disease and a first-degree relative with breast cancer at ≤ 40
- **All ages**
 - Clearly apparent family history and/or other risk factors indicating appropriate increased risk of breast cancer for age

Target Accrual: 6,000

Study Contacts

Cancer Research UK Clinical Trials Unit at University of Glasgow
Jack Cuzick, PhD, Study Coordinator
International Breast Cancer Study Group
Katharina Buser, MD, Principal Investigator

SOURCES: CRUK-IBIS-II Prevention Protocol, July 2005; ibis-trials.org. NCI Physician Data Query, October 2006; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► NSABP-B-35 and IBIS-II are important trials, both comparing anastrozole and tamoxifen in postmenopausal patients with DCIS. Aromatase inhibitors have already proved to have a significant effect in invasive cancer, and it's highly likely they will affect DCIS as well.

We know that the majority of DCIS lesions are likely to be ER-positive. Craig Allred has shown that age-per-age, tumor-for-tumor, DCIS is even more likely to be ER-positive than invasive cancer. If that's true, then we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

We have viewed tamoxifen as a highly appropriate

option for treating a patient with ER-positive DCIS since the NSABP-B-24 trial.

However, when we consider risks, benefits and quality-of-life issues, it's common for our New York patients to demur, so we probably have one of the lowest percentages of patients with ER-positive DCIS on tamoxifen in the country.

The same can be seen in our prevention setting, in which we've not been successful in getting patients to take tamoxifen.

The two most obvious concerns about tamoxifen in these settings are endometrial cancer and gynecological events. Even when we provide the raw numbers on how infrequent those events are,

because we are talking about minimal, if any, impact on long-term survivorship and moderate impact on local control, it simply is not an attractive option.

We'd like more information about DCIS and aromatase inhibitors, but since the initial publication of the ATAC data, aromatase inhibitors have become our endocrine therapy of choice for postmenopausal patients with ER-positive, invasive cancers. That literally happened overnight, like gangbusters, and so a "bleed over" to postmenopausal patients with DCIS is natural.

In my clinical practice, it's clear that the aromatase inhibitors are vastly better tolerated than tamoxifen in postmenopausal patients. Our surgeons are beginning to give first-line endocrine therapy without a mandatory consult from medical oncology. We perform bone density tests before we start our patients on aromatase inhibitors, and treating these patients has been satisfying. ■

— Patrick I Borgen, MD

► There is still uncertainty about what constitutes adequate local treatment, and much remains to be done to delineate the various subtypes of DCIS and to ascertain the minimum adequate treatment for each. However, the case for hormonal treatment of oestrogen or progesterone receptor-positive DCIS is already strong and, accordingly,

we have focused our attention on which hormonal treatment — tamoxifen or anastrozole — is best for this subgroup of patients. For IBIS II, women with DCIS have up to 6 months to decide about entry, so there is plenty of time for discussion and no rush to make this important decision. ■

— Jack Cuzick et al.
Lancet 2003;362:832-3.

► The IBIS-II prevention trial compares the aromatase inhibitor anastrozole to placebo. We'll all be surprised if anastrozole does not reduce the incidence of breast cancer. Although we're currently fixated on the bone effects associated with the aromatase inhibitors, I believe we will find that with the new, powerful bisphosphonates, the bone effects will not be a long-term problem.

One of the strengths of the IBIS-II prevention trial is that it will help identify women for whom we need to do bone scans and those with whom we need to use bisphosphonates. In the separate bone subprotocol of the IBIS-II prevention trial, women with a high baseline bone mineral density (BMD) won't receive a bisphosphonate, women with a low baseline BMD will automatically receive a bisphosphonate and women with a baseline BMD in the midrange will be randomly assigned to a bisphosphonate or placebo. ■

— J Michael Dixon, MD

SUPPORTING PROTOCOL INFORMATION

Background Information

DCIS was once a rare diagnosis, but it has become increasingly common following the advent of mammographic screening. Radiotherapy has been shown to reduce local recurrence rates by 60-70%, but there is still uncertainty as to which group of patients require this rather intensive treatment. Adjuvant endocrine therapy has also been advocated, and there are two trials which have addressed this issue. The North American NSABP-B-24 trial looked at the value of giving tamoxifen to women who had received radiotherapy. A highly significant 37% reduction in recurrence rate was found. However, the recently completed UK trials have not been so positive, reporting a non-significant 17% reduction in recurrence. The clear benefit of tamoxifen in the adjuvant studies, even for early stage 1 disease also provides strong support for an effect of hormonal therapy in DCIS. The focus

of the current trial will be to evaluate whether the aromatase inhibitor anastrozole has advantages over tamoxifen, either in terms of reduced recurrence rates or lower side effects.

Correlative Science Program

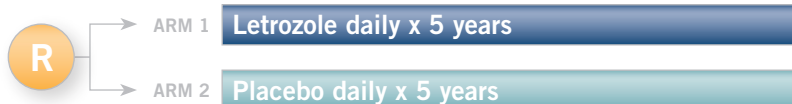
A set of representative diagnostic H&E stained slides plus the original hormone receptor assay slides (ER and/or PgR) will be required from all patients for central review. Paraffin blocks containing representative areas of the tumour will also be requested.

Diagnostic slides and paraffin blocks will be requested for all breast, endometrial or ovarian cancers developing after trial entry. These samples will be used for central pathology review and marker studies, and will remain the property of the Steering Group, who will be responsible for deciding how they will be used in any further projects.

NSABP-B-42

A Phase III trial to determine improvement in disease-free survival with adjuvant letrozole following completion of five years of hormonal therapy with either an aromatase inhibitor (AI) or tamoxifen followed by an AI

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Postmenopausal
- No later than six months from completion of five years of hormonal therapy consisting of either five years of an AI or up to three years of tamoxifen followed by an AI for a total of five years
- ER-positive and/or PR-positive
- Invasive breast cancer

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Survival, recurrence-free interval, distant recurrence-free interval, osteoporotic fracture rate, arterial thrombosis

Target Accrual: 3,840 over 5.25 years

Current Accrual: 1 (10/02/06)

Date Activated: August 14, 2006

Study Contact

National Surgical Adjuvant Breast and Bowel Project
Eleftherios Mamounas, MD, MPH
Protocol Chair

SOURCES: NSABP-B-42 Protocol, July 2006; nsabp.pitt.edu.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► NSABP-B-42 just opened. It has a sample size of about 3,800, and of course one of the questions that remains unanswered is the duration of an aromatase inhibitor.

We went through this process and it took us years to determine the optimum duration of tamoxifen therapy, and at the end of the day there was enormous surprise from the B-14 data that not only is 10 years not as good as five, but it is also somewhat detrimental.

We believe it's important to address the duration of an aromatase inhibitor, and this is what NSABP protocol B-42 will be doing.

The data with aromatase inhibitors from the multiple trials have all been positive. The duration question remains relatively unaddressed. We have seen trials that have introduced aromatase inhibitors after a period of tamoxifen and have shown an advantage.

We've seen direct head-on comparisons between

aromatase inhibitors and tamoxifen up front also showing an advantage, and we're waiting to see the results of a trial that starts with an aromatase inhibitor and sequences it with tamoxifen. ■

— Norman Wolmark, MD

► The problem with the extended letrozole trial (NCIC-CTG-MA17) was that the patients were unblinded at 2.4 years, and because most patients then switched over to the active agent, we will never know with any certainty what would have happened had they been unblinded at five years.

That is a shame because we are going to be treating these patients for five years, so it would have been nice to know the differences in toxicity and efficacy between the two arms.

The data for one or two years are complete because most of the patients had gone through those years. There were a lot of data in year

three, a modest amount in year four and almost no data for the fifth year.

An analysis of relapse risk within each year could then be performed. This was possible not only for years one and two but also for year three, when it seems that the relative benefit was greater, which is interesting and reassuring. That was also the case in year four. That analysis used year-by-year

hazards to determine whether benefit was attenuating, staying as strong or becoming stronger. Although we will never know what it would have been if the trial had been unblinded at five years, we are somewhat reassured by the results of this analysis that going beyond 2.4 years of treatment is reasonable. ■

— Peter M Ravdin, MD, PhD

SUPPORTING PROTOCOL INFORMATION

Background Information

In the adjuvant setting, AIs have demonstrated activity in three distinct clinical situations. In the first situation, an AI was compared to tamoxifen as initial adjuvant hormonal therapy in patients with resected operable breast cancer.

The ATAC trial demonstrated that 5 years of anastrozole significantly improved disease-free survival (DFS) when compared to 5 years of tamoxifen. More recently, the BIG 1-98 trial also demonstrated improved DFS as well as distant DFS for 5 years of letrozole compared to 5 years of tamoxifen.

In the second situation, an AI was compared to tamoxifen in patients who had already received 2-3 years of adjuvant tamoxifen. In three randomized trials (the IES trial [International Exemestane Study], the ABCSG-8/ARNO 95 trial, and the ITA trial [Italian Tamoxifen vs Anastrozole]), 2-3 years of an AI (exemestane or anastrozole) improved disease-free survival compared to 2-3 years of tamoxifen in patients who had already completed 2-3 years of tamoxifen therapy.

In the third clinical situation, an AI was evaluated as extended adjuvant hormonal therapy following completion of 5 years of adjuvant tamoxifen. The NCIC-MA17 trial compared 5 years of letrozole with 5 years of placebo in patients who had already completed 5 years of adjuvant tamoxifen and demonstrated significant improvement in disease-free survival in favor of the group that received the AI...

Based on the results from these trials, AIs are increasingly utilized as adjuvant therapy in these three clinical situations. At this time, there are no available results from trials that directly compare these different approaches for using AIs. Thus, the best setting for the adjuvant use of AIs cannot be readily determined at present...

As the adjuvant use of AIs continues to expand, the question of optimal duration needs to be definitively addressed. Whether less than 5 years of an AI given as up-front adjuvant therapy is as effective as 5 years is a question that is unlikely to be addressed, given that in the pivotal ATAC trial, 5 years of anastrozole were found to be

superior to 5 years of tamoxifen. On the other hand, whether prolonged administration of an AI beyond 5 years will result in additional benefit is an important and clinically relevant question that is currently not being addressed in any clinical trial. It is quite possible that resistance to AIs in this setting may develop at different time intervals than resistance to tamoxifen...

Similarly, in the clinical situation where the AI is given for 2-3 years following 2-3 years of adjuvant tamoxifen, it is also unknown whether continuing the AI for more than 2-3 years might result in additional benefit...

Finally, no data exist on the optimal duration of AIs when used as extended adjuvant therapy after 5 years of tamoxifen. Five years of therapy was arbitrarily selected in the MA17 trial, but whether shorter therapy could be as effective or whether longer therapy could be more effective are questions that need to be addressed.

Correlative Science Program

We will be banking paraffin blocks from the primary tumor (or positive lymph node) in order to have an opportunity to evaluate promising markers in the future, if they become available. At this point, there are some data that suggest a differential benefit from an AI over tamoxifen based on the molecular profile of tumor cells. These data suggest that a certain subset of breast cancer patients might not derive maximum benefit from five years of tamoxifen and derive greater benefit from an AI.

It could be hypothesized that such patients may derive greater benefit if the AI is given for a longer duration. We will examine ER, PR, and HER2 by standardized central assays. We will explore quantitation of ER and PR by an image analysis program to examine the correlation between expression levels and benefit from the longer duration of an AI.

Abnormalities involving cofactors for ER signaling such as AIB1 may result in resistance to tamoxifen but not to an AI. Patients with such tumors can be hypothesized to benefit even more with a longer duration of an AI.

CFEM345D2411

A comparison trial of anastrozole versus letrozole in the adjuvant treatment of postmenopausal women with hormone receptor-positive, node-positive breast cancer

TRIAL DESIGN

ARM 1 Anastrozole daily x 5 years

ARM 2 Letrozole daily x 5 years

KEY FACTS**Select Eligibility Criteria**

- Node-positive disease
- ER-positive or PR-positive disease

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Safety, efficacy, overall survival, breast cancer-specific survival, time to development of distant metastases

Target Accrual: 4,000

Date Activated: December 2005

SOURCES: NCI Physician Data Query, October 2006; cancer.gov.

CAN-NCIC-MA27

A comparison trial of anastrozole versus exemestane in the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer

TRIAL DESIGN

ARM 1 Anastrozole daily x 5 years

ARM 2 Exemestane daily x 5 years

KEY FACTS**Select Eligibility Criteria**

- Invasive breast cancer
- ER-positive and/or PR-positive
- T1-3b by clinical and pathological evaluation

Primary Endpoint

- Event-free survival

Secondary Endpoints

- Overall survival, recurrence-free interval, distant recurrence-free interval, clinical fracture rate, cardiovascular morbidity and mortality, therapy-induced changes, toxicities

Target Accrual: 6,840

Current Accrual: 7,134 (10/01/06)

Date Activated: June 2, 2003

Study Contact

NCIC-Clinical Trials Group

Paul Goss, MD, PhD, Protocol Chair

SOURCES: NCI Physician Data Query, October 2006; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► As the safety data for the aromatase inhibitors are emerging, we see they are quite different. In the package insert for exemestane, a small but definite increased risk of cardiac dysfunction is noted. If you consider the letrozole data from the BIG trial, at 25 months a small but definite increased risk of cerebrovascular accident and myocardial infarct is evident.

However, in the 68-month follow-up data for the ATAC trial, we see none of those risks with anastrozole. If you examine the cardiac deaths, it is 49 versus 46, and cerebrovascular accidents are substantially reduced with anastrozole compared to tamoxifen.

An interesting study presented at the 2005 San Antonio Breast Cancer Symposium evaluated 90 healthy, postmenopausal volunteers who received, in a blinded fashion, up to 24 weeks of either anastrozole, letrozole or exemestane. When the effects on the lipids were examined, they were found to be totally different.

We have to be aware of the different effects and realize that not all aromatase inhibitors are alike and that it does matter which one we select. ■

— Aman Buzdar, MD

► A significantly reduced risk of thromboembolic disease was observed for all three AIs compared with tamoxifen. Anastrozole is, at this point, the only AI with a detailed benefit-risk profile from over 5 years' follow-up in the adjuvant setting.

Thus far, no apparent CV-safety concerns have emerged. Preliminary data on letrozole and exemestane suggest that longer follow-up is needed for these two AIs before being able to fully assess their respective long-term CV toxicity profile.

The present differences in CV-safety profiles suggest that third-generation AIs should not be considered as equivalents in clinical practice. ■

— Jean Marc Nabholz, Joseph Gligorov.
Drug Saf 2006;29(9):785-801.

► There may be important clinical differences between the AIs. However, data from direct comparative clinical trials are limited, and making comparisons across trials is difficult given differences in design, methodology, patients, and endpoints. At the present time, the choice of an AI for clinical use should be based on the

strength of the data within the distinct clinical scenarios: neoadjuvant therapy, adjuvant therapy, or advanced/metastatic disease. ■

— John W Berry, MD.
Clin Ther 2005;27(11):1671-84.

► The aromatase inhibitor I would choose for initial treatment would be either anastrozole or letrozole. Following two to three years of tamoxifen, it would be exemestane or anastrozole, and after five years of tamoxifen, it would be letrozole.

My expectation is that the aromatase inhibitors, as a class, are going to be active in all of those settings, but we don't know that for sure and subtle differences in the adjuvant setting sometimes emerge in surprising ways. So at this time, I would favor using one of the aromatase inhibitors that has been used in clinical trials. ■

— Robert W Carlson, MD

► We don't know what the appropriate approach is to selecting one of the three aromatase inhibitors in the up-front setting. I have the good fortune of chairing a key study to this regard.

The MA27 study will complete accrual in 2006, and it is addressing precisely that question of whether there is an optimal aromatase inhibitor. The randomization is between the steroidal exemestane and the nonsteroidal anastrozole.

In the meantime, there are ample data to say these compounds are different in terms of their biochemical and preclinical effects. But in the clinic, with the present data, there is no evidence of a wide difference between these drugs. So I think that one has to restrict one's choices to the approved therapies by the regulatory agencies and the published evidence-based data. ■

— Paul E Goss, MD, PhD

► As time goes on, there is less and less of a distinction to be made between the aromatase inhibitors. Up front, I don't have a strong preference. There are certainly data for anastrozole and letrozole.

I tend to use anastrozole simply because it has longer safety data. There we have the largest number of patients that have been followed, so in my mind, there's more confidence in the safety profile. ■

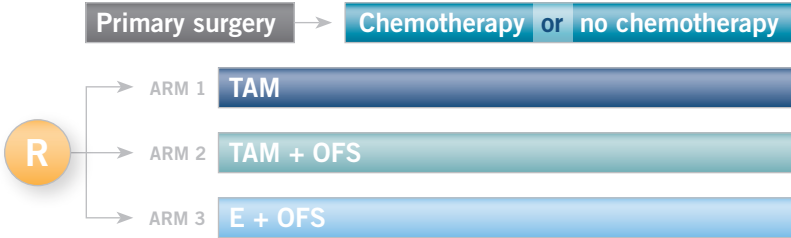
— Debu Tripathy, MD

SOFT/TEXT/PERCHE

TRIAL DESIGNS

SOFT (IBCSG-24-02)

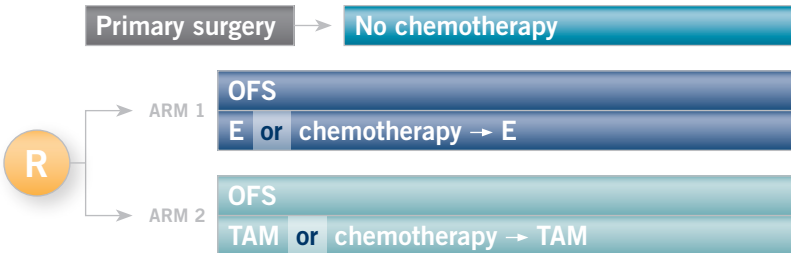
Phase III randomized study of ovarian function suppression (OFS) in combination with tamoxifen versus OFS in combination with exemestane (E) versus tamoxifen (TAM) alone in premenopausal women with endocrine-responsive resected breast cancer



SOURCES: IBCSG-24-02 Protocol v2.0; ibcsg.org.

TEXT (IBCSG-25-02)

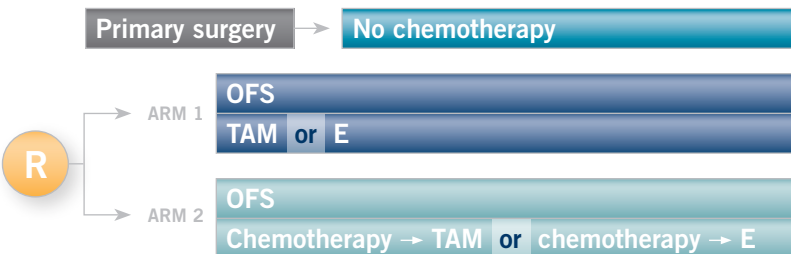
Phase III randomized study of OFS and exemestane versus OFS and tamoxifen in premenopausal women with endocrine-responsive resected breast cancer



SOURCES: IBCSG-25-02 Protocol v2.0; ibcsg.org.

PERCHE (IBCSG-26-02)

Phase III randomized study of OFS and tamoxifen or exemestane with or without adjuvant chemotherapy in premenopausal women with endocrine-responsive resected breast cancer



SOURCES: IBCSG-26-02 Protocol v2.0; ibcsg.org.

SOFT KEY FACTS

Select Eligibility Criteria

- Premenopausal
- Tumor confined to the breast and axillary nodes
- Resected breast cancer
- ER-positive and/or PR-positive

Stratification

- Intended initial method of ovarian function suppression, if assigned by randomization (LHRH agonist for five years; surgical oophorectomy; ovarian irradiation)
- Institution
- Prior chemotherapy (no; yes)
- Number of positive nodes (0; ≥ 1)

Other Therapy

- Patients may have received tamoxifen or an antiaromatase agent prior to randomization
- Prior and/or concurrent adjuvant trastuzumab allowed

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Overall survival, disease-free survival at five years, quality of life as measured by menopausal symptoms

Target Accrual: 3,000

Current Accrual: 767 (09/30/06)

Date Activated: August 4, 2003

Study Contacts

International Breast Cancer Study Group
Prudence Francis, MD, Protocol Chair

Breast International Group
Prudence Francis, MD, Protocol Chair

Cancer and Leukemia Group B
Gini Fleming, MD, Protocol Chair

TEXT KEY FACTS

Select Eligibility Criteria

- Premenopausal
- Tumor confined to the breast and axillary nodes
- Resected breast cancer
- ER-positive and/or PR-positive

Stratification

- Institution
- Concurrent adjuvant chemotherapy (no; yes)
- Number of positive nodes (0; ≥ 1)

Other Therapy

- Prior and/or concurrent adjuvant trastuzumab allowed

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Overall survival, disease-free survival at five years, quality of life, sites of first treatment failure, incidence of second (nonbreast) malignancies

Target Accrual: 1,845

Current Accrual: 1,148 (09/30/06)

Date Activated: August 4, 2003

Study Contacts

International Breast Cancer Study Group
Olivia Pagani, MD, Protocol Chair

Breast International Group
Olivia Pagani, MD, Protocol Chair
Prudence Francis, MD, Protocol Chair

PERCHE KEY FACTS

Select Eligibility Criteria

- Premenopausal
- Tumor confined to the breast and axillary nodes
- Histologically confirmed resected breast cancer
- ER-positive and/or PR-positive ($\geq 10\%$ positive cells by IHC)

Stratification

- Institution
- Number of positive nodes (0; ≥ 1)
- Intended initial method of ovarian function suppression (LHRH agonist for five years; surgical oophorectomy; ovarian irradiation)
- Intended chemotherapy if assigned by randomization (not containing anthracycline or taxane; containing anthracycline or taxane)
- Intended endocrine agent (selected by subsequent randomization in the TEXT trial [recommended option]; tamoxifen; exemestane)

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Overall survival, systemic disease-free survival, quality of life, site of first treatment failure, incidence of second (nonbreast) malignancies

Target Accrual: 1,750 within seven years

Current Accrual: Not reported

Date Activated: August 4, 2003

Study Contacts

International Breast Cancer Study Group
Rosalba Torrissi, MD, Protocol Chair

Breast International Group
Rosalba Torrissi, MD, Protocol Chair

COMMENTS FROM BREAST CANCER INVESTIGATORS

► For premenopausal women with endocrine-responsive disease, we initiated three adjuvant trials in August 2003: the Suppression of Ovarian Function Trial (SOFT), the Tamoxifen and Exemestane Trial (TEXT) and the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE).

SOFT will compare tamoxifen alone to ovarian function suppression with tamoxifen and ovarian function suppression with exemestane. This trial was designed specifically for oncologists who view tamoxifen as standard therapy.

TEXT will compare ovarian function suppression with tamoxifen to ovarian function suppression with exemestane. These patients may or may not receive chemotherapy.

PERCHE will determine whether adjuvant chemotherapy is necessary. Premenopausal women are randomly assigned to chemotherapy or no chemotherapy. Adjuvant chemotherapy selection is left entirely up to the investigator, and endocrine therapy consists of ovarian function suppression with tamoxifen or exemestane. Patients may also be randomly assigned to TEXT for endocrine therapy. ■

— Aron Goldhirsch, MD

► TEXT assumes that women need or should undergo ovarian suppression as part of their treatment protocol. The randomization is then between tamoxifen and an aromatase inhibitor. We tend to think of tamoxifen as the standard of care for young, premenopausal women with breast cancer, and the big controversy is whether or not ovarian suppression or ovarian ablation has a role.

In fact, a fair amount of information exists to suggest that it does have a role. First, the Oxford overview with oophorectomy/ovarian irradiation suggests that, by itself, this is very good adjuvant therapy. If you go back to those old trials, you see approximately a 10 percent absolute change in mortality. Second, we have a lot of information comparing ovarian suppression, with or without tamoxifen, to chemotherapeutic regimens in patients with receptor-positive tumors. In many European trials, those two approaches are basically equivalent, although they are imperfectly conducted trials. Third, we have trials that have examined whether or not you should use ovarian suppression after chemotherapy. The results are mixed right now. The trials in aggregate don't show a clear-cut advantage for

this approach. However, from the point of view of retrospective subset analyses, a feeling does emerge from a couple of the trials that perhaps the younger women who were premenopausal at the end of chemotherapy and then received ovarian suppression are the ones who might be helped the most.

The problem with all of these trials is that they started in the late 1980s before we recognized that tamoxifen was a valid choice for young women with breast cancer. All of these studies lacked five years of tamoxifen, which is now the standard of care. I believe that is a fundamental flaw of these trials that we wish had been addressed.

Putting this all together is very complicated, and I don't think I know the answer to the question. That is one reason why I'm such a strong proponent of SOFT, which evaluates tamoxifen versus ovarian suppression or ablation with tamoxifen versus ovarian suppression or ablation with an aromatase inhibitor. I believe this trial would help us to answer some of these questions that are a terrific struggle for us. ■

— Nancy E Davidson, MD

► The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These trials address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients?

In particular, does it benefit women who receive chemotherapy or who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression? These are important trials that offer a wonderful opportunity for community oncologists to participate in answering this critical question.

Currently, I consider ovarian suppression for two groups of patients. The first group includes patients at high risk — multiple positive nodes, very high-risk tumors — and particularly young women, less than 35 or 40 years of age, who may not go into menopause with chemotherapy. The other group includes women who are at the opposite end of the spectrum — very low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are small. With these women, I present ovarian suppression as an option, not necessarily in addition to chemotherapy but perhaps even instead of it. ■

— Harold J Burstein, MD, PhD

SWOG-S0307

A Phase III randomized study of adjuvant zoledronate versus clodronate versus ibandronate for women with resected primary Stage I-III adenocarcinoma of the breast

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Stage I-III breast cancer
- Creatinine ≤ 2 times upper limit of normal
- Creatinine clearance ≥ 30 mL/min
- Lumpectomy or mastectomy within the past 12 weeks
- No metastases
- No enrollment on protocols that measure bone density as an endpoint
- No concurrent bisphosphonates
- Standard adjuvant therapy

Endpoints

- Disease-free survival, overall survival, first disease recurrence, adverse events, parathyroid hormone-related protein status, N-telopeptide levels

Primary Hypothesis

This study proposes to determine whether two newer, potentially more potent bisphosphonates, zoledronic acid and ibandronate, can delay or prevent the occurrence of metastases compared to the control arm containing oral clodronate.

Target Accrual: 6,000 within 4 years

Current Accrual: 171 (9/29/06)

Date Activated: July 15, 2005

Study Contacts

Southwest Oncology Group

Julie Gralow, MD, Study Coordinator
Robert Livingston, MD, Study Coordinator

North Central Cancer Treatment Group

James Ingle, MD, Study Coordinator

Eastern Cooperative Oncology Group

Carla Falkson, MD, Study Coordinator

National Surgical Adjuvant Breast

and Bowel Project

Alexander Paterson, MD, FRCP, FACP, MBChB
Study Coordinator

Cancer and Leukemia Group B

Elizabeth Dees, MD, Study Coordinator

NCIC Clinical Trials Group

Mark Clemons, MD, Study Coordinator

SOURCES: SWOG Protocol S0307, June 12, 2006; swog.org.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► Adjuvant bisphosphonates are of great interest to us because of a few intriguing European trials that showed a probable survival benefit to adding oral clodronate at bone metastasis doses to treatment for early-stage breast cancer. In two

of three European trials, a survival benefit is still apparent at 10 years. Clodronate was never approved in the United States for any indication, neither for treatment nor prevention of bone metastasis, so the NSABP-B-34 study, with

3,000 patients, was designed to examine the adjuvant question.

We hope to have those results in the next couple of years. The 10-year update of the European data was reported at the time we were designing SWOG-S0307 as the successor to the B-34 study, so we chose clodronate as the control arm, which is unconventional because it is not our standard of care in the United States. Ibandronate is another oral bisphosphonate chosen for the study, at a dose of 50 mg daily, and the third study arm is IV zoledronic acid administered monthly for the first six months and then quarterly.

Eligibility requires a high enough risk of recurrence to require treatment with endocrine therapy, chemotherapy or both. We are allowing coenrollment on virtually any other trial as long as that

trial doesn't specifically preclude it. Registration may start within 12 weeks of final surgery or chemotherapy.

For corollary studies, we are asking patients at the beginning and end of the study about their preference for receiving medication intravenously versus orally. It will be interesting to see how the different arms respond. We are also tracking patients closely to make sure that osteonecrosis of the jaw is not happening.

We're also carefully monitoring renal function across all of the groups to see how renal function might be affected, and we are collecting blood and a tumor block from the time of the initial diagnosis in an attempt to look for things that would predict for a pattern of bone recurrence versus other sources of recurrence. ■

— Julie R Galow, MD

SUPPORTING PROTOCOL INFORMATION

Background Information

Three randomized clinical trials of the oral bisphosphonate clodronate as adjuvant therapy in breast cancer have been reported, yielding conflicting results with respect to development of bone metastases and survival...

The German trial continues to show a survival benefit for the clodronate arm (80% vs 60%), with overall survival at 103 months, $p = 0.04$. The final analysis of the larger UK-led trial shows a statistically significant survival benefit for the clodronate arm, with a hazard ratio for survival of 0.768 ($p = 0.048$) that persists at 10 years of follow-up. The 10 year follow-up of the Finnish study found no significant survival difference between the groups. The intriguing but contradictory results of these three adjuvant bisphosphonate studies highlight the need for further investigation to determine whether bisphosphonates can influence the development of bone metastases and improve survival in early stage breast cancer.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has recently completed accrual on a multicenter confirmatory trial. NSABP-B-34 is evaluating oral clodronate for three years versus placebo in addition to standard treatment in 3,200 patients with Stage I or II breast cancer.

The North American Intergroup trial S0307 will compare newer, more potent bisphosphonate agents to clodronate. It is noteworthy that this trial design will still be valid even if the B-34

study results are not able to show a benefit for clodronate. As long as the clodronate arm is not inferior to placebo in B-34 (which is fairly unlikely provided the weight of the available evidence), the clodronate arm of the proposed trial would serve as a "reference control" against which one could still study the two newer, more potent bisphosphonates.

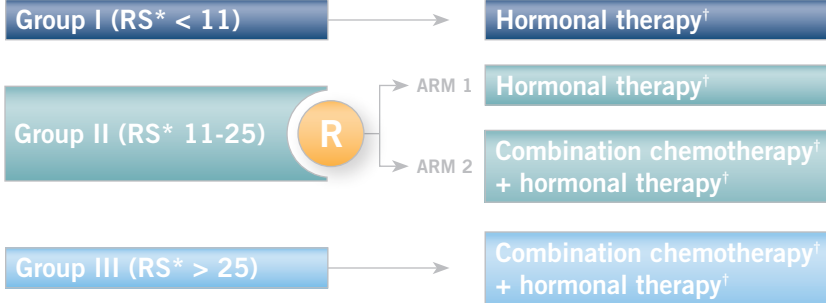
Clodronate is approved in Canada, Europe and Asia at the 1,600 mg per day dose for treatment of bone metastases and has been widely used for greater than a decade. It is on fast-track approval with the FDA in the US....Ibandronate has recently been approved in Europe, Central America and Asia for the treatment of bone metastases in both intravenous form (6 mg dose monthly) and oral form (50 mg daily)...Zoledronic acid is approved in the United States at the dose to be used in S0307 for the treatment of bone metastasis in multiple myeloma and all solid tumors.

Some patients may prefer oral formulations to IV formulations for reasons of comfort and convenience. Zoledronic acid is available only as an intravenous infusion, whereas ibandronate may be given either intravenously or as an oral tablet. While oral bioavailability of bisphosphonates is overall very low ($\leq 0.5-4\%$), it has been shown that oral dosing of ibandronate resulting in comparable drug exposure to effective intravenous doses can be achieved and that this dose is tolerable and efficacious in inhibiting skeletal-related events.

TAILORx

A Phase III randomized trial of adjuvant combination chemotherapy and hormonal therapy versus adjuvant hormonal therapy alone in women with previously resected axillary node-negative breast cancer with an intermediate score of the Oncotype DX assay

TRIAL DESIGN



* Oncotype DX recurrence score

† Physician's choice for hormonal therapy and chemotherapy

KEY FACTS

Select Eligibility Criteria

- ER-positive and/or PR-positive breast cancer
- Negative axillary nodes
- Tissue from primary tumor available for Oncotype DX assay
- 18-75 years of age
- HER2-negative
- Tumor size 1.1-5.0 centimeters (tumors 5 mm to 1.0 cm allowed if intermediate or poor nuclear and/or histologic grade or lymphovascular invasion)

Stratification for Group II

- Tumor size (≤ 2.0 cm, ≥ 2.1 cm)
- Menopausal status (post, pre, peri)
- Chemotherapy (taxane, nontaxane)
- Radiation therapy (whole breast without boost, whole breast with boost, partial breast irradiation, none [those having undergone a mastectomy])

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Distant recurrence-free interval, recurrence-free interval, overall survival

Target Accrual: 10,046

Date Activated: April 7, 2006

Study Contacts

Eastern Cooperative Oncology Group
Joseph Sparano, MD, Protocol Chair

Southwest Oncology Group
Daniel Hayes, MD, Protocol Chair

Cancer and Leukemia Group B
Elizabeth Dees, MD, Protocol Chair

American College of Surgeons Oncology Group
John Olson, MD, PhD, Protocol Chair

North Central Cancer Treatment Group
Edith Perez, MD, Protocol Chair

NCIC Clinical Trials Group
Kathleen Pritchard, MD, Protocol Chair

National Surgical Adjuvant Breast and Bowel Project
Charles Geyer, FACP, MD, Protocol Chair

SOURCES: PACCT-1 Protocol, August 23, 2006; ecog.org.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► The PACCT trial is pointing us in the direction of therapeutic individualization. We've known for a long time that some of the relatively low-risk group of patients who are estrogen receptor-positive and lymph node-negative will benefit from the addition of adjuvant chemotherapy to adjuvant hormonal therapy. Based on studies from the 1980s and 1990s, we know that four or five women out of 100 will be alive and disease-free a decade out if they receive adjuvant chemotherapy in this setting. What that automatically tells you is that we're vastly overtreating patients and the great majority of patients derive no benefit from the addition of chemotherapy to hormonal therapy. In the past, we've always needed to treat an entire population to benefit a few.

If the trial is successful, this will be the first time in a prospective, large, clinical, randomized trial that we have used modern genomic technology to help us determine therapies for patients. This will get us much closer to our goal of therapeutic individualization for patients. Our hope is to avoid unnecessary toxicity for patients who are going to do well without chemotherapy and, at the same time, pick out those patients who will receive clear survival benefit from the addition of adjuvant chemotherapy. That's a very exciting change. ■

— George W Sledge Jr, MD

► Using archival tissue blocks from past trials, Genomic Health and Dr Soon Paik analyzed about 200 genes that were reported to possibly relate to outcome in breast cancer. They narrowed that set down to just 16 genes that could be sorted into logical groups based on the estrogen receptor, the HER2 protein and proliferation and invasion characteristics of the cells.

That set of 16 genes plus five reference genes were used to see if breast cancer patients could be sorted into prognostic and predictive groups. When I say "prognostic" I mean to predict the likelihood of recurrence, and when I say "predictive" I mean to predict patients who would benefit from chemotherapy.

So these investigators examined the archival subsets and were able to determine that those 16 genes and five reference genes could be used to sort patients along a continuum they called the recurrence score, which varies from zero to 100. Using simple mathematic regression procedures, that recurrence score could then be translated

into a probability of recurrence over 10 years.

The investigators were able to determine that patients who had low recurrence scores — that is, scores of 18 or lower — benefited from hormonal therapy but derived no additional benefit from the addition of chemotherapy to their hormonal therapy regimens. Conversely, patients with high recurrence scores — scores of 31 or higher — showed a clear, statistically significant and large benefit when cytotoxic chemotherapy was added to hormonal therapy — that is, tamoxifen. In the intermediate group, the group with scores between 18 and 30, no benefit was apparent from the addition of chemotherapy, but the confidence intervals — the statistical certainty of no benefit — were not established.

What came out of that work was the *Oncotype* DX assay from Genomic Health. It is commercially available and essentially allows selection of patients for hormonal therapy alone or hormonal therapy with chemotherapy in the high-risk group. In the intermediate-risk group, we're left with some uncertainty. An Intergroup clinical trial, known as the TAILORx study, is for patients with ER-positive, node-negative, early-stage — Stage I, small Stage II — breast cancer. Patients will be randomly assigned to chemotherapy or no chemotherapy, in addition to their hormonal therapy, if they fall into that intermediate-risk group. ■

— Victor G Vogel, MD

► NSABP-B-20 included women with node-negative, ER-positive disease. It had a three-arm design, and patients were randomly assigned to tamoxifen alone or tamoxifen concurrent with either CMF or methotrexate followed by 5-FU. Our study was a retrospective analysis of that completed trial. We only had tissue blocks available for approximately 30 percent of the entire study cohort, so it's a subset, but the subset and the entire cohort were comparable. We repeated the *Oncotype* DX assay on the tamoxifen arm to ensure the assay was reproducible, and we demonstrated that it is reproducible, which is encouraging.

Importantly, we evaluated the chemotherapy arms to address whether the *Oncotype* DX assay recurrence score predicted chemotherapy responsiveness. We went into that study with an *a priori* hypothesis, based on the data presented at ASCO 2004 by Dr Luca Gianni's group from Milan evaluating samples from a neoadjuvant trial they

performed with paclitaxel and doxorubicin.

They demonstrated a correlation between the Genomic Health recurrence score and pCR rate. The higher recurrence rate correlated strongly with the higher pCR rate. The overall pCR rate was approximately 25 percent among the patients with high-risk disease, and no pCR occurred in patients with low-risk disease. We hypothesized that the benefit from chemotherapy in NSABP-B-20 would be almost negligible in patients with low-risk disease and high in patients with high-risk disease.

The results of this study are quite striking and unlike anything I've ever seen. The absolute benefit from chemotherapy is zero in the low-risk group and zero in the intermediate-risk group. In the high-risk group, the absolute improvement in distant recurrence at 10 years is 28 percent, or a relative risk reduction of 75 percent. The data with the low-risk group are, in a sense, not relevant because the baseline risk after tamoxifen is so low — 6.8 percent — that it's a moot point whether they need chemotherapy or not. In the intermediate-risk group the confidence interval overlaps with one, so whether patients with intermediate-risk disease gain any benefit or not remains a question.

These data provide an important paradigm shift in the way we think about clinical trial design and patient management. So far, in most clinical trial designs, we have presumed that the proportional benefit or incremental gain would be the same degree for patients with low-risk and high-risk disease. All statistical sample size calculations are based on that assumption, but now we have to change that. It forces us to think about the clinical trial designs by which we preselect patients who are at high risk because those are the patients who will benefit. We already knew from other studies that patients with ER-positive disease do not benefit much from chemotherapy.

In the neoadjuvant trials, the pCR rate is much lower for ER-positive tumors. This study definitely shows that, based on genes related to proliferation or estrogen receptor, we can select patients who are the best candidates for chemotherapy trials. ■

— Soonmyung Paik, MD

▶ In the B-20 study, patients with an intermediate recurrence score also did not seem to derive much benefit. The 10-year distant recurrence-free survival was approximately 90 percent both for patients treated with tamoxifen alone and

those treated with tamoxifen and chemotherapy.

However, in that group of patients, the confidence intervals around the estimates were somewhat wide, so we could not exclude some benefit. In fact, the odds ratio was about 0.6, so a reduction of up to 40 percent is possible.

What was interesting was that the benefit was seen in the patients with a high recurrence score. Among those patients, the absolute improvement in distant disease-free survival with chemotherapy was 28 percent, or a 75 percent relative reduction in the odds of recurrence. The group that received tamoxifen alone had a 60 percent distant disease-free survival rate at 10 years, and it was 88 percent for the group that received tamoxifen with chemotherapy. We've never seen such differences in any subset of patients with breast cancer. I like to quote what George Sledge said when he saw these data: "This makes CMF look like a targeted regimen." That's true. In other words, we found a signature that predicts a huge benefit from a regimen that otherwise was almost ready to become obsolete. ■

— Eleftherios P Mamounas, MD, MPH

▶ The reason we are conducting the TAILORx trial is that we are in enormous equipoise about the addition of chemotherapy for the intermediate group. I believe we all agree that the addition of chemotherapy for the low recurrence score group is below our radar screen in terms of benefit, and most of us also agree that patients with high recurrence scores have at least a five to six percent or higher absolute reduction in recurrence rates. Those are the patients for whom we would probably recommend chemotherapy.

But for the intermediate group, whether we define it as a recurrence score of 11 or 18, we are in great equipoise. That is especially true because the aromatase inhibitors may be more effective than tamoxifen, so patients have a better prognosis than the patients in the NSABP study. I also believe that doxorubicin and the taxanes will be more effective in patients with lower ER and higher HER2 levels.

So depending on where you are in that intermediate group, you may have a better prognosis than we think you have, but you may have a higher proportional reduction than that achieved with CMF. The randomized portion of that trial is critical. ■

— Daniel F Hayes, MD

▶ The TAILORx trial is following up on the findings of the value of the *Oncotype DX* assay

in assessing the risk of recurrence and predicting the benefit from chemotherapy. It's an interesting and ambitious trial that is scientifically compelling and something we would like to see completed. ■

— Norman Wolmark, MD

► The TAILORx trial is meant to ask a very practical question borne of the data that have been generated by Genomic Health evaluating a limited number of genes in paraffin-embedded tissue. The real-time quantitative PCR is used to generate a score of the risk of recurrence for

patients with early-stage, ER-positive, node-negative breast cancer. Based on that score, one can make decisions about adding chemotherapy to the standard hormone therapy that is given.

The TAILORx trial focuses our attention in the areas where we have the greatest degree of uncertainty. We are now asking that question in an identified subset of patients where we would predict that the risk of recurrence is modest and the benefits of chemotherapy are modest. Therefore, it's important to determine whether there is benefit. ■

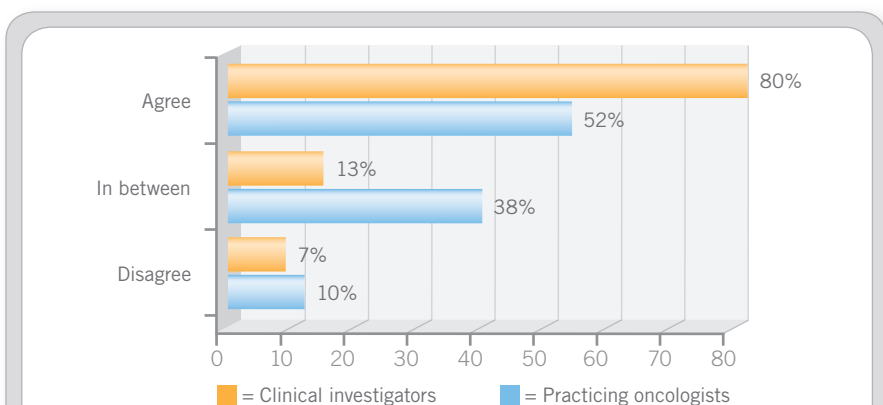
— Clifford Hudis, MD

SUPPORTING PROTOCOL INFORMATION

Although several distinct molecular signatures identified by differing methodologies have been developed that may serve as useful prognostic markers, we have chosen to utilize the *OncoType* DX Breast Cancer Assay in this trial for the following reasons: 1) it is a standardized, multi-gene RT-PCR-based molecular technique performed in a single laboratory, 2) it may be applied to tissue specimens routinely processed in clinical pathology laboratories, 3) it has received CLIA approval in the United States to "...assess the likelihood that a women's breast cancer will...recur..." (genomichealth.com), 4)

it more reliably predicts prognosis than standard clinical criteria in patients with ER-positive, node-negative disease than standard clinical criteria, including tumor size, histologic grade and age, 5) its performance has been validated in a large population-based study, and 6) preliminary data indicate that it predicts benefit from adjuvant chemotherapy. Patients with ER-positive, axillary node-negative breast cancer account for nearly one half of all breast cancer diagnosed in the United States, and this is the group in which more patients unnecessarily receive adjuvant chemotherapy.

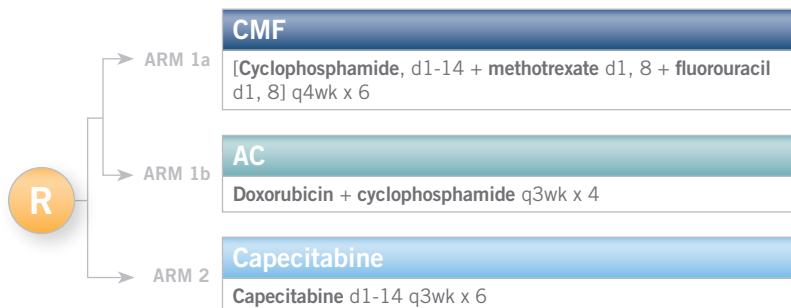
For patients with ER-positive, HER2-negative, node-negative tumors, the *OncoType* DX assay should be offered when both the doctor and patient are "on the fence" about whether to use adjuvant chemotherapy.



SOURCE: Survey of 45 Breast Cancer Clinical Investigators and 150 US-Based Practicing Oncologists (June 2006); Love N; Research To Practice. **Management of breast cancer in the adjuvant and metastatic settings.** *Patterns of Care in Medical Oncology* 2006;3(1).

CALGB-49907

A Phase III randomized study of cyclophosphamide, methotrexate and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) versus oral capecitabine in elderly women with operable adenocarcinoma of the breast

TRIAL DESIGN**KEY FACTS****Select Eligibility Criteria**

- Age ≥ 65
- Stage I-IIIc breast cancer
- T1-4, N0, M0 or T1-4, N1-3, M0
- HER2-positive or HER2-negative
- Performance status 0-2
- Creatinine clearance ≥ 30 mL/min

Stratification

- HER2 status (positive versus negative versus unknown)
- Age (65-69 versus 70-80 versus over 80)
- Performance status (0-1 versus 2)

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Overall survival, quality of life and physical function, toxicity and adherence by older patients to an oral chemotherapy regimen

Choice of Chemotherapy

Patients with insufficient left ventricular ejection fraction (LVEF) are assigned to Arm 1a (CMF). Patients with normal LVEF are assigned to Arm 1a or 1b (AC) based on physician/patient choice.

Patients with estrogen receptor-positive or progesterone receptor-positive disease receive oral tamoxifen or an aromatase inhibitor daily for five years.

Beginning four to six weeks after treatment, eligible patients who previously had breast

conservation surgery undergo radiation therapy.

Use of Trastuzumab

Adjuvant trastuzumab will be allowed following protocol chemotherapy only for patients whose tumors are HER2-positive by either IHC 3+ staining or gene amplification by FISH. A 52-week course of trastuzumab will be permitted for all patients with HER2-positive disease after completion of protocol chemotherapy. The concurrent use of chemotherapy and trastuzumab is not acceptable.

Trastuzumab should not begin until at least three weeks after but within eight weeks of the last dose of chemotherapy. For patients who have already completed chemotherapy, trastuzumab can be initiated up to six months from the completion of chemotherapy.

Target Accrual: 1,800 within 2-6 years

Current Accrual: 592 (9/28/06)

Date Activated: September 15, 2001

Study Contacts

Cancer and Leukemia Group B

Hyman Muss, MD, Protocol Chair

Eastern Cooperative Oncology Group

Antonio Wolff, MD, Protocol Chair

Southwest Oncology Group

Julie Gralow, MD, Protocol Chair

NCIC-Clinical Trials Group

Debjani Grenier, MD, Protocol Chair

SOURCES: CALGB 49907/CTSU 49907 Protocol, May 15, 2006; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► We're excited about the trial, which is an equivalence study. Some preliminary data suggest that oral capecitabine is as good as standard therapy in metastatic disease. It would be nice if we had an oral regimen because I think people would rather be at home than in our clinics all the time. We have a quality-of-life endpoint, and we're collecting data from approximately the first 300 patients. We're also going to collect tumor blocks to see if we can predict how these older patients do with chemotherapy.

In CALGB-49907, capecitabine is given at a dose of 2,000 mg/m² per day in divided doses for 14 consecutive days every three weeks for six cycles. We initially escalated the dose to 2,500 mg/m², but we elected to reduce it because of severe toxicity. I believe this lower dose is certainly adequate.

Based on our experience with a dihydropyrimidine dehydrogenase-deficient patient, we amended the protocol to identify these patients. We now have women come in between days four and six of the first cycle and again several days later for "mini checks." We do this to make sure we don't miss patients who may have profound toxicity early. These checks will enable us to stop the drug early and avoid serious toxicity. Our assessment is that capecitabine is a reasonably safe drug, but patients need to be informed. Doctors who don't frequently use capecitabine need to

be aware of this early toxicity, and older patients should be contacted and assessed.

We are gathering excellent quality-of-life data and collecting adherence data with an electronic pill bottle. We are also evaluating some incredible laboratory science, including genes that might tell us about toxicity, such as levels of thymidine phosphorylase, thymidylate synthase and dihydropyrimidine dehydrogenase. We'll be storing all the blocks for future work.

Although it's a little early for me to predict how to compare these regimens, I believe patients may perceive that capecitabine is a little easier to take because it is oral and not associated with alopecia. ■

— Hyman B Muss, MD

► In addition to the more familiar ER, PR and HER2 markers, we are evaluating some interesting predictive and prognostic markers and other biological markers.

We are also examining how these drugs are metabolized in the elderly population. The data from the metastatic setting provided the rationale for selecting capecitabine for this trial — these trials compared capecitabine to single-agent paclitaxel and to CMF and demonstrated benefits from capecitabine in time to progression. ■

— Maria Theodoulu, MD

SUPPORTING PROTOCOL INFORMATION

Background Information

Women 70 years and older are not represented in current adjuvant trials. In the meta-analysis of 18,000 women entered into randomized trials of adjuvant chemotherapy, only 600 patients (3%) 70 years and older were entered into these trials. Although this sample size was insufficient to determine the benefits of chemotherapy in this age group, combination chemotherapy regimens significantly lowered the risk of recurrence by 20% (SD 3%) and the risk of dying of breast cancer by 11% (SD 3%) in patients 50 to 69 years.

Since it is unlikely that the proportional benefits of chemotherapy for patients age 70 years and older are different than for postmenopausal women 50 to 69 years old, there is no reason to suspect that older women would not have similar risk reductions.

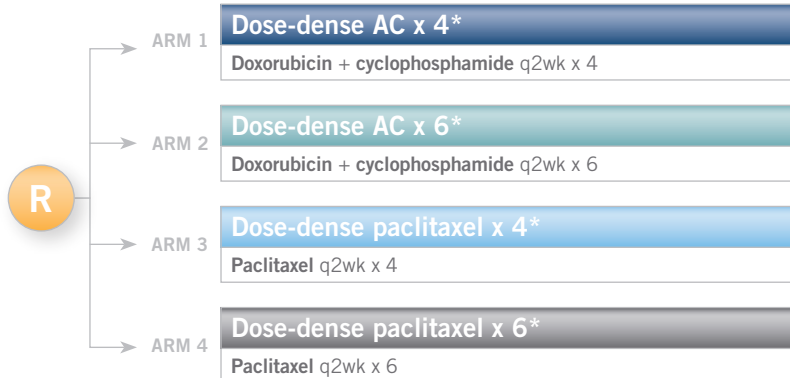
A recent randomized phase II trial, comparing

single agent capecitabine and CMF as first-line therapy in patients with metastatic breast cancer who were 55 years and older (median age 69 years), demonstrated that the response rate to capecitabine alone (25%) at a dose of 2,510 mg/m² per day for 14 days every 3 weeks was superior to intravenous CMF (16%). Grade 3 or 4 hand-foot syndrome was seen in 16% of patients on capecitabine and none on CMF, grade 3 or 4 diarrhea in 8% with capecitabine and 3% with CMF, and grade 3/4 hematological toxicity in 20% with capecitabine and 47% with CMF. In another phase II randomized trial comparing capecitabine in the same dose and schedule as above with paclitaxel 175 mg/m² every three weeks, the response rate was 36% for 22 patients on capecitabine and 21% for 22 patients on paclitaxel. These data suggest that the efficacy of capecitabine in patients with metastatic disease is similar to CMF or paclitaxel.

CALGB-40101

A Phase III randomized study of two different schedules of adjuvant cyclophosphamide and doxorubicin versus paclitaxel

TRIAL DESIGN



*Growth factor support: Filgrastim or sargramostim recommended days 3-10 of each cycle. Pegfilgrastim may be substituted and should be given 24 to 36 hours after the administration of chemotherapy.

KEY FACTS

Select Eligibility Criteria

- Zero to three positive lymph nodes or high-risk node-negative to warrant chemotherapy
- HER2-positive, HER2-negative or unknown
- Any estrogen or progesterone receptor status
- No locally advanced or inflammatory disease

Primary Endpoint

- Disease-free survival (DFS)

Secondary Endpoints

- Survival, local control, distant recurrence-free interval, toxicity, menopause induction, myelosuppression in MDR1 haplotypes, DFS in MDR1 haplotypes, correlation of polymorphisms with DFS and toxicity

Target Accrual: 4,646 within 29 months

Current Accrual: 2,523 (9/28/06)

Date Activated: May 15, 2002

Study Contact

Cancer and Leukemia Group B
Lawrence Shulman, MD, Protocol Chair

SOURCES: CALGB 40101/CTS0 40101 Protocol May 15, 2006; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► Compared to the AC regimen that is widely used in the adjuvant setting, paclitaxel offers a couple of advantages. It should not cause congestive heart failure, which is a very specific anthracycline toxicity. Second, it may not cause the same long-term risk of leukemia and myelodysplastic syndromes that are seen with AC. We therefore sought to determine whether we could substitute single-agent paclitaxel for AC in patients at lower risk.

The second component of CALGB-40101 asked a more basic question, which was whether a few more cycles of chemotherapy are better than a few less. So this study not only compares paclitaxel versus AC, it also compares four cycles of therapy versus six.

After this study began, we received the results for CALGB-9741, which identified the benefits of giving chemotherapy every two weeks rather than every three weeks with the important advan-

tages of improvements in disease-free and overall survival and the shortening of time that patients are on therapy. There was also the paradoxical but important result that the every other-week chemotherapy is a bit less toxic than the every

third-week therapy. We therefore modified 40101 so that it was symmetrical and even, with every patient getting simply every two-week therapy, four or six cycles, AC or paclitaxel. ■

— Clifford Hudis, MD

SUPPORTING PROTOCOL INFORMATION

Background Information

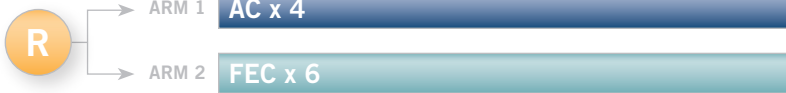
Adjuvant trastuzumab will be allowed only in patients whose tumors are HER2 positive by either IHC 3+ staining or gene amplification by FISH... A fifty-two week course of trastuzumab

will be permitted for all HER2-positive patients. For patients enrolled in the paclitaxel arms, trastuzumab may be administered concurrently with paclitaxel. The concurrent use of an anthracycline and trastuzumab is not acceptable.

NSABP-B-36

Phase III randomized study of adjuvant fluorouracil, epirubicin and cyclophosphamide versus doxorubicin and cyclophosphamide

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Node-negative breast cancer
- Hormone receptor-positive or hormone receptor-negative
- Primary tumor T1-3 by clinical and pathologic evaluation

Stratification

- Receptor status (ER-positive or PR-positive; ER-negative and PR-negative)
- Type of surgery (lumpectomy, total mastectomy)

Other Therapy

Patients with ER-positive and/or PR-positive tumors will receive hormonal therapy beginning no sooner than three weeks and no later than 12 weeks following the last dose of chemotherapy and continuing for a minimum of five years.

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Survival, recurrence-free interval, distant recurrence-free interval, HER2 and TOPO II gene amplification, postchemotherapy amenorrhea, changes to LVEF and quality of life

- Toxicities

Target Accrual: 2,700 within 3.75 years

Current Accrual: 1,625 (10/2/06)

Date Activated: May 20, 2004

Study Contact

National Surgical Adjuvant Breast and Bowel Project

Richard Elledge, MD, Protocol Chair

SOURCES: NSABP-B-36 Protocol, February 7, 2006; nsabp.pitt.edu.

SUPPORTING PROTOCOL INFORMATION

Background Information

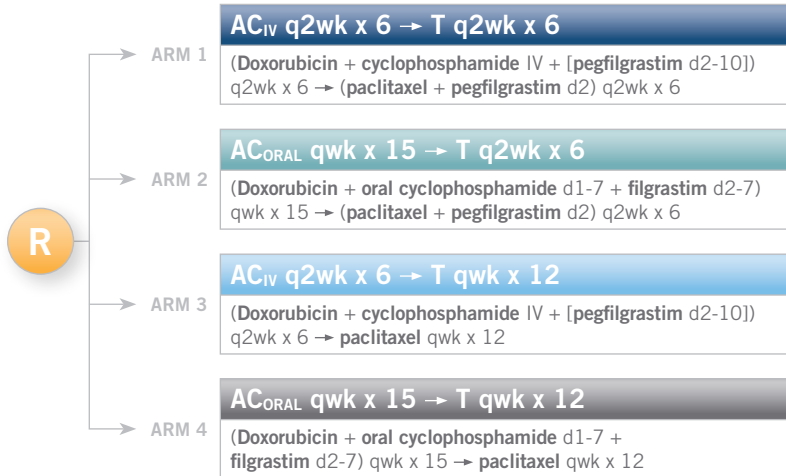
On the basis of findings from our previously published studies of NSABP trials B-11 and B-15 as well as from other published studies, we hypothesize that clinical benefit from six cycles of FEC over four cycles of AC may be restricted

to a cohort whose tumors have amplification of HER-2 and/or topoisomerase-2-alpha (Topo-II). Tissue microarrays will be generated from the submitted blocks and FISH (fluorescence in-situ hybridization) will be used to examine the presence or absence of gene amplification for HER2 and Topo-II.

SWOG-S0221

A randomized trial of four schedules of adjuvant doxorubicin, cyclophosphamide and paclitaxel in patients with node-positive or high-risk node-negative breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Stage I-III invasive breast cancer
- ER and PR status known
- HER2-negative or HER2-positive
- Node-negative disease with tumor ≥ 2 centimeters OR node-positive disease

Other Therapy

Patients with HER2-positive disease receive trastuzumab administered weekly or every three weeks concurrently with paclitaxel or three months following the last dose of paclitaxel for up to one year.

Patients with ER-positive or PR-positive disease receive hormonal therapy within 28 days following the completion of adjuvant chemotherapy or radiation therapy (if administered).

Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Overall survival and adverse events

Primary Hypothesis

“Metronomic” AC is superior to AC administered according to an accelerated but more conventional schedule. We predict that patients treated with AC + growth factors will have a longer disease-free and overall survival than patients treated with conventional AC.

Weekly paclitaxel is superior to the administration of this agent every two weeks with filgrastim support. We predict that treatment with weekly paclitaxel will produce a longer disease-free and overall survival than will treatment with paclitaxel administered every two weeks with filgrastim or support when administered following AC.

Target Accrual: 4,500 within 2.25 years

Current Accrual: 1,352 (9/29/06)

Date Activated: November 1, 2003

Study Contacts

Southwest Oncology Group
 George Budd, MD, Study Coordinator
 Halle Moore, MD, Study Coordinator

SOURCES: SWOG-S0221 Protocol, October 7, 2005; swog.org.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► In the SWOG-0221 study, AC is administered in either a dose-dense manner with pegfilgrastim or what might be described as a metronomic schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control arms for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment.

Data suggest six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other anti-angiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule, a burst of vasculogenesis occurs between cycles. Hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide. ■

— **G Thomas Budd, MD**

► The initial trial design of SWOG-S0221 was based on two small pilot studies that demonstrated that highly dose-dense therapy for 20 to 24 weeks — with weekly doxorubicin and daily oral cyclophosphamide requiring G-CSF support — produced promising results in patients with node-positive disease. Patients with a median of four positive nodes had an 86 percent five-year disease-free survival, which compared favorably to the standard NSABP AC regimen in a similar population.

Then the results of CALGB-9741 changed the landscape of clinical research in the adjuvant setting. Members of the Intergroup share a strong desire to build upon that trial, which showed the every two-week administration of AC and paclitaxel, with G-CSF support, was better than the every three-week schedule.

The logical next step would be a comparison of every two-week AC and our weekly doxorubicin and daily cyclophosphamide regimen — “dose dense versus dose denser.” The evaluation of weekly paclitaxel was suggested by the outcome of the MD Anderson neoadjuvant study, which randomly assigned patients to every three-week versus weekly paclitaxel, with the FAC component constant in both arms. A major advantage was seen in the pathologic complete response — 28 versus 14 percent — for patients who received weekly paclitaxel.

Growth factor support is used in each arm of

the trial. Pegfilgrastim — the pegylated form of G-CSF — is utilized in the every two-week arms, and patients treated with the weekly doxorubicin and daily cyclophosphamide regimen will receive filgrastim because we do not have experience with pegfilgrastim and concurrent chemotherapy and the FDA will not allow it.

The study is a two-by-two factorial design. We will not have enough statistical power to formally test for superiority of each of the four arms, but we have more than enough power to test for the weekly versus every two-week approaches, which was the same statistical approach taken in CALGB-9741. The study will accrue approximately 4,500 patients, which is almost twice as many as CALGB-9741. ■

— **Robert B Livingston, MD**

► The SWOG-S0221 study builds upon CALGB-9741, but it makes several important modifications. First, it assumes that six cycles are better than four, so the baseline is six cycles of dose-dense AC followed by six cycles of paclitaxel, every two weeks.

Using a factorial design and random assignment, half the patients will receive the metronomic schedule for AC, which is a regimen that involves weekly low-dose doxorubicin and oral daily cyclophosphamide. Some preoperative data are showing a very high response rate for patients treated with that regimen specifically, and there are reasons to hypothesize that it could be superior.

The study will also address whether low-dose weekly paclitaxel for twelve weeks might be superior to every two-week therapy the way that it was superior to every three-week therapy. The SWOG study is a very important effort that allows us to “dot the Is and cross the Ts” about whether there is an optimal way to deliver these drugs to patients. ■

— **Clifford Hudis, MD**

► SWOG-S0221 is an adjuvant trial for what we’re calling patients at high risk — generally they have node-positive disease but could also have node-negative disease if they have a higher than average risk. It’s a two-by-two design asking what is the best way to administer an anthracycline-based combination and what is the best way to administer a taxane.

It’s modeled after the CALGB dose-dense experience. So for the standard arm with both the

AC and the paclitaxel, the question is an every two-week AC or an every two-week paclitaxel. The experimental arm is a metronomic dosing schedule that was piloted in Seattle and then through SWOG, in which the anthracycline is administered in a smaller weekly dose.

The cyclophosphamide is oral and is administered continuously on a daily basis. The taxane section is weekly. So AC dose dense versus AC metronomic is one question, and paclitaxel every two weeks at the 175 mg/m² dose versus paclitaxel weekly at the 80 mg/m² dose is another.

We're interested in whether there is potential with this lower, metronomic, continuous dosing to have an even greater impact maybe not solely on the tumor cells but also on the angiogenic properties of the tumor environment.

Currently, we're seeing more neutropenia with the dose-dense AC, which we're administering with pegfilgrastim, than we are with the metronomic regimen, which we're administering with filgrastim six out of seven days a week.

I will remind you that for a variety of complicated reasons, the AC and the taxane dose-dense schedule are administered for six rather than four cycles. So it is an expansion of the dose-dense concept with a few extra cycles.

The decision part-way through the development of the study was that they did not want the time on the study drug to be different, so they added a

few more cycles of the AC and the taxane. ■

— Julie R Gralow, MD

► This Intergroup trial SWOG-S0221 compares a regimen of oral cyclophosphamide and a weekly anthracycline to the dose-dense every two-week doxorubicin and cyclophosphamide (AC) regimen used in CALGB-9741. It also compares dose-dense every two-week to weekly paclitaxel.

Frankly, I don't know which regimens will be better, and I have pure equipoise on this study. The trial is not as clean a comparison as the one in CALGB-9741, in which all the doses were kept exactly the same and only the schedule was varied. For the dose-dense regimens, the additional expense associated with filgrastim and pegfilgrastim is a real and important concern. ■

— Larry Norton, MD

► SWOG-S0221 is an important study, particularly with regard to the best way to administer paclitaxel. Weekly paclitaxel is an interesting regimen, and it's logical to compare it to a dose-dense regimen that is probably more expensive.

On the other hand, weekly paclitaxel will require weekly visits to the hospital, which might not be easy. In the meantime, ECOG-1199 provides a head-to-head comparison of every three-week paclitaxel, every three-week docetaxel, weekly paclitaxel and weekly docetaxel. ■

— Martine J Piccart-Gebhart, MD, PhD

SUPPORTING PROTOCOL INFORMATION

Correlative Science Program

Tissue blocks will be obtained to serve as a resource for future correlative studies. Examples of such studies might include the following: tumor microvessel density or tumor VEGF expression by immunohistochemistry.

The inferior survival outcomes of women of African ancestry (AA) with breast cancer after adjustment for multiple variables mandates exploration of treatment details, molecular, biologic, pharmacogenetic and hormonal hypotheses. To lay the groundwork for future studies, we will further explore the etiology of the observed ethnic/racial differences in breast cancer outcomes. This project will address differences in estrogen synthesis and metabolism and variability in chemotherapeutic drug metabolism as factors in racial differences in survival.

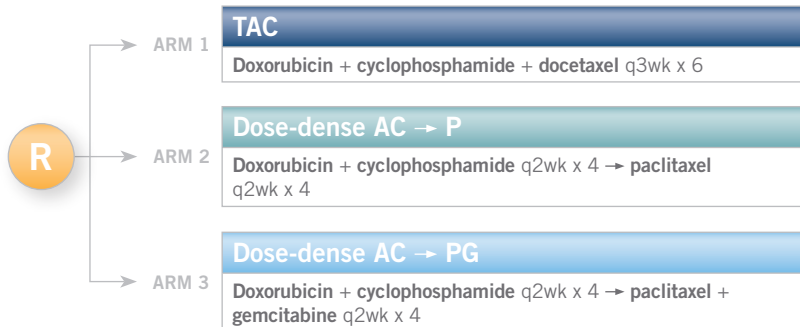
There is widespread use of antioxidants and other dietary supplements among cancer patients, used with the intentions and hopes that supplement use will maintain overall health, decrease treatment-associated toxicity and increase treatment efficacy. However, there are no existing empirical data to support the notion that antioxidant supplement use can decrease toxicity associated with treatment, and it is unclear if vitamin use has any impact on treatment efficacy, either to inhibit it or to enhance it.

We will query women enrolled in this study about supplement use and evaluate it in relation to toxicity and recurrence. We will also evaluate if variants (polymorphisms) in genes that impact levels of oxidative stress will affect toxicity and disease-free survival or modify relationships between supplement use and treatment outcomes.

NSABP-B-38

A Phase III adjuvant trial comparing three chemotherapy regimens in women with node-positive, HER2-negative breast cancer

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Node-positive invasive breast carcinoma
- T1-3 by clinical and pathologic evaluation
- Hormone receptor-positive or hormone receptor-negative
- HER2-negative

Stratification

- Number of positive nodes (1-3, 4-9, 10+ nodes)
- Hormone receptor status (ER-negative and PR-negative; ER-positive and/or PR-positive)
- Type of surgery and planned radiation therapy

Other Therapy

Primary prophylaxis with pegfilgrastim or filgrastim is required.

Women with ER-positive and/or PR-positive tumors will begin hormonal therapy no sooner than three weeks and no later than 12 weeks following the last dose of chemotherapy.

Primary Endpoint

- Disease-free survival (DFS)

Secondary Endpoints

- Survival, recurrence-free interval, distant recurrence-free interval, toxicities

Primary Hypothesis

In the design of this trial, we have adopted the position that, at the current time, both TAC and DD AC → P are considered “standard” treatment options in this patient population. Therefore, two primary statistical hypotheses will be evaluated in this trial:

- Is DD AC → PG superior to both TAC and DD AC → P with respect to DFS?
- Is there a difference in DFS between TAC and DD AC → P?

Target Accrual: 4,800 within 4 years

Current Accrual: 3,503 (10/2/06)

Date Activated: October 1, 2004

Study Contact

National Surgical Adjuvant Breast and Bowel Project

Sandra Swain, MD, Protocol Chair

SOURCES: NSABP-B-38 Protocol, October 26, 2005; nsabp.pitt.edu.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► NSABP-B-38 is a very practical study. At the time we designed this trial, we talked a lot about also studying bevacizumab. Even before the data

for ECOG-E2100 came out, we were excited about bevacizumab and thought that would be the biologic agent that would be important for

the adjuvant setting. However, the drug was not felt to be ready for the adjuvant setting. So we decided to ask a practical question.

The dose-dense data had been presented and showed a one or two percent survival benefit, and that seemed to be a popular regimen, with more than half the country using it.

We also considered the BCIRG 001 data evaluating TAC versus FAC, which showed a very positive result with much longer follow-up. At that time, I felt that the docetaxel was a more effective taxane, not having the ECOG-E1199 data yet.

So we decided to compare TAC to dose-dense chemotherapy. Then Kathy Albain presented gemcitabine/paclitaxel data, which showed a small survival benefit when you add gemcitabine. We decided to have another arm so we could improve outcomes, if possible, if the dose-dense regimen turned out to be best or equivalent to TAC.

When the adjuvant trastuzumab data came out, we decided to exclude patients who were HER2-positive. We didn't have that many patients on the trial who were HER2-positive to begin with, because the NSABP-B-31 study was running concurrently and most of the patients would have gone on that study. ■

— Sandra M Swain, MD

▶ BCIRG 001, evaluating TAC versus FAC, and the CALGB-9741 dose-dense trial of AC/paclitaxel are two key adjuvant trials. Currently, our view is that TAC appears to be the optimal way to administer an anthracycline/docetaxel regimen, and dose-dense AC/paclitaxel is the optimal way to administer those agents.

Which is better? It's impossible to answer that question without performing a clinical trial, which is why we developed NSABP-B-38.

It's a pragmatic design in which we regard TAC as our control arm. A clear advantage of dose-dense therapy is that it is so well tolerated, and it affords the opportunity to add a fourth drug to the paclitaxel. TAC is a maximally tolerated regimen. You really can't push it much more, so we sought a candidate drug to combine with paclitaxel. ■

— Charles E Geyer Jr, MD

▶ NSABP-B-38 was motivated by the debate and controversy surrounding the optimal chemotherapy regimen for treating node-positive disease. The concept of dose density, which

came to the forefront in 2002, has made remarkable headway from a popularity standpoint. The real question in our minds was whether we can incorporate it and compare it to what others consider to be a standard of care, which is the TAC regimen.

So we have a three-arm trial in which, in essence, the control arm is six cycles of TAC compared to "Nortonian" dose-dense chemotherapy and the third arm attempts to improve on the regimen by adding a gemcitabine doublet, also given in a dose-dense regimen.

This trial has been popular. It started in October 2004, and the required sample size is approximately 4,800. To date, we have more than 3,300 patients accrued. ■

— Norman Wolmark, MD

▶ A paper in *Seminars in Oncology* in the mid-1980s indicated that the primary problem in Gompertzian growth is not cell kill but rather regrowth between cycles.

While therapy gets us closer to the cure limits, you have to get below a small number of cells to prevent regrowth, and regrowth occurs faster as you move away from that limit.

A rebound effect is evident, and the key is to inhibit that regrowth. One of the simplest ways to address regrowth is to move the doses of therapy close enough together to have less regrowth between cycles.

This is extremely powerful in Gompertzian kinetics, as long as you can drive the tumor toward that cure limit. In the adjuvant setting, when you're probably close to the cure limit, you can achieve dramatic benefits by giving the doses closer together in time. ■

— Larry Norton, MD

▶ On the basis of the available data, one can consider TAC to be a standard of care, as is the dose-dense regimen of doxorubicin and cyclophosphamide followed by paclitaxel, for patients with resected node-positive breast cancer. However, the exclusion of patients older than 70 years and the toxic effects associated with TAC in the BCIRG trial cannot be minimized. With this regimen, prophylactic growth-factor support is necessary to ameliorate myelosuppression and febrile neutropenia.

A recommendation for the selection of one regimen over the other must await completion of the prospective National Surgical Adjuvant

Breast and Bowel Project trial B-38, for which the accrual of data is expected to be complete in the next few years. ■

— Edith A Perez, MD.

N Engl J Med 2005;352(22):2346-8.

▶ I believe that TAC without growth factors is more toxic than dose-dense AC. We have data from a trial in Spain in which Miguel Martin treated node-negative disease with TAC or FAC. Early in the trial they thought, “For node-negative disease, TAC is quite tough,” and they mandated G-CSF.

At that point, they found that the tolerability increased dramatically. It’s not a randomized trial, and it’s an intervention halfway through, but they found that not only did the febrile neutropenia rate drop, but the mucositis, fatigue and diarrhea decreased as well.

In addition, the quality-of-life decrements that come with chemotherapy were less after G-CSF was initiated.

I agree that “naked” TAC without growth factors is probably tougher than dose-dense therapy with growth factors. However, I believe that difference would be much less if you used primary prophylaxis with pegfilgrastim or filgrastim. I would

suggest that if you are going to use it, use it with growth factor support. ■

— John Mackey, MD

▶ When people say that the addition of dose-dense scheduling in CALGB-9741 doesn’t yield much among patients with ER-positive disease, they’re not comparing apples to apples when they then assess the TAC-FAC data.

The TAC-FAC trial demonstrated hazard rates for risk reductions, which looked about the same in the ER-positives and the ER-negatives. The FAC control arm, of course, includes no paclitaxel or docetaxel.

You can’t say that each individual step is or is not significant vis-à-vis another separate randomized trial. You can’t compare these regimens head to head. If you were to argue that you know to use TAC instead of dose-dense AC → paclitaxel for a patient with ER-positive, node-positive disease, then you’re presuming to know the results of NSABP-B-38.

I would argue that there is equipoise on this question and that either regimen is entirely appropriate for patients with ER-positive disease. ■

— Clifford Hudis, MD

SUPPORTING PROTOCOL INFORMATION

Background Information

In a sense, TAC represents the current optimal program of a taxane, doxorubicin, and cyclophosphamide combination. DD AC → P represents the current optimal program of a sequential taxane following a doxorubicin and cyclophosphamide program...

Clearly, a risk reduction of 20%-25% in disease-free survival with one regimen relative to the other would provide differentiating information based on efficacy. This study will be powered to demonstrate those differences if they are present.

However, if the regimens do not differ in relative efficacy by that magnitude, the major determinate of clinical utility would be relative toxicity, and direct comparison in a randomized trial will provide that information...

Although the TAC and DD AC → P regimens have improved treatment outcome, unfortunately women treated with either regimen still develop local, regional, and systemic disease recurrence. This reality provides a compelling reason to continue efforts to further improve therapy for

node-positive breast cancer.

One potential advantage of DD AC → P is that its reported toxicity profile provides opportunity for incorporating a fourth chemotherapeutic agent into the program by adding it to the paclitaxel sequence.

The anti-metabolite gemcitabine has shown promise in combination with paclitaxel for treatment of metastatic breast cancer using various schedules, including every 2-week dosing intervals.

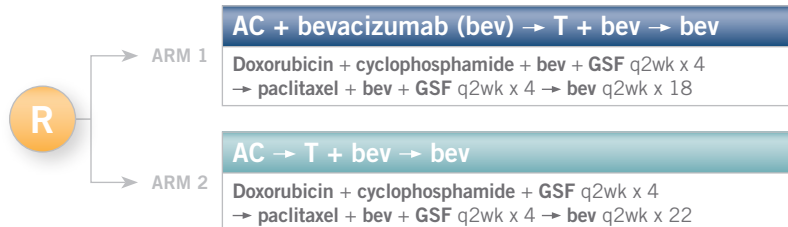
Correlative Science Program

The NSABP has an ongoing correlative science program that is attempting to identify prognostic factors for node-positive patients treated with 4 cycles of AC, as well as predictive factors for benefit from additional chemotherapeutic agents such as paclitaxel, docetaxel, and gemcitabine.

To support this important work, tissue block submission will be mandatory for all patients who have given consent for tissue submission so complete tissue arrays can be developed for this trial.

ECOG-E2104

A Phase II study of adjuvant bevacizumab and dose-dense doxorubicin and cyclophosphamide followed by paclitaxel in patients with resected lymph node-positive breast cancer

TRIAL DESIGN**KEY FACTS****Select Eligibility Criteria**

- Node-positive, HER2-negative breast cancer

Primary Endpoint

- Cardiac dysfunction rate

Secondary Endpoints

- LVEF changes, noncardiac toxicity

Target Accrual: 212

Date Activated: October 6, 2005

Study Contacts

Eastern Cooperative Oncology Group

Kathy Miller, MD, Protocol Chair

Robin Zon, MD, Protocol Co-Chair

North Central Cancer Treatment Group

Edith Perez, MD, Protocol Chair

SOURCES: ECOG-E2104 Protocol, November 16, 2005; ecog.org.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► The ECOG-E2104 pilot adjuvant trial is critically important because it will evaluate adding bevacizumab to an anthracycline-based treatment regimen.

The trial will enroll 212 patients, and the chemotherapy regimen is dose-dense AC followed by paclitaxel. ECOG-E2104 is observing two different cohorts.

The first cohort receives bevacizumab with the anthracycline and throughout therapy. The second cohort receives bevacizumab only with paclitaxel, and this is our backup if we do see cardiac toxicity issues with the combined administration. Hence, we'll have safety data with both strategies.

The full adjuvant trial will use a slightly different chemotherapy backbone that won't require

growth factors. We will be using AC on an every three-week basis followed by weekly paclitaxel. I wanted to use a weekly taxane regimen because the biggest support for moving this into the adjuvant setting is the data from ECOG-E2100, which used a weekly taxane schedule.

The proposed full adjuvant trial (ECOG-E5103) has three arms, on which everybody receives the same chemotherapy. Patients in arm A receive no bevacizumab. Those in arm B receive six months of bevacizumab, concurrently with chemotherapy, and those in arm C receive 12 months of bevacizumab, six months with chemotherapy and an additional six months of maintenance.

The first six months of therapy are blinded and placebo controlled. At the end of the chemotherapy treatment, patients and their physicians

will be told to which arm they have been assigned and whether they're continuing bevacizumab for an additional six months.

With regard to the signal seen in E2100, we expect much greater activity in the adjuvant setting, and recent laboratory data suggest that we're likely to see it. First-line chemotherapy for metastatic disease is fairly late in the natural history of breast cancer.

Although the patients in the E2100 trial hadn't received chemotherapy for metastatic disease, two thirds of them had received adjuvant chemotherapy, and 18 percent had received a taxane. These were not chemotherapy-naïve patients. They were much more advanced than the patients enrolled a decade ago in trials of first-line chemotherapy for metastatic disease. ■

— **Kathy D Miller, MD**

► We know relatively little about bevacizumab and the heart, and this, of course, remains an issue. Certainly, with trastuzumab, clinicians and laboratory scientists were absolutely astonished when trastuzumab was found to increase congestive cardiomyopathy with anthracycline-based chemotherapy, and that was due to a lack of understanding of the biology of the disease.

We have a number of small studies, and these typically involve 20 to 40 patients, where patients have received bevacizumab in combination with an anthracycline or with an anthracenedione, and in a number of these studies, there is just barely a hint of some increased rate of congestive cardiomyopathy.

The problem with these studies is that they tend to be in populations of patients who are already at increased risk for congestive cardiomyopathy in that, in addition to anthracyclines, they frequently will have undergone prolonged use of anthracyclines up to a larger dose in the metastatic setting than we would ever use in the adjuvant setting. These patients frequently will have undergone left chest wall irradiation. So we're simply not sure whether or not this is a true signal or a false one. ECOG-E2104 was designed to answer this question. This is a pilot adjuvant trial in which patients in the first part of the trial receive doxorubicin and cyclophosphamide followed by paclitaxel, administered in a dose-dense fashion, and patients receive bevacizumab from the beginning with careful cardiac monitoring before, during and following the year's period of bevacizumab.

The second part of this trial is only evaluating bevacizumab in combination with paclitaxel but,

again, with the same careful cardiac monitoring. The trial is not powered to pick up tiny signals. It's powered to pick up fairly significant signals. But the first half of the trial has completed accrual, and we expect to have at least some initial data from this in a fairly short time period.

The National Cancer Institute will be taking data from this trial and combining it with two smaller Phase II trials in which an anthracycline has been combined with bevacizumab to get some sense of the rate of congestive cardiomyopathy.

If that rate is significant, then what we would do in the large randomized trial would be to give bevacizumab solely with the paclitaxel. We're hoping, of course, that won't be the case. ■

— **George W Sledge Jr, MD**

► We're anxiously awaiting the safety analysis of ECOG trial E2104. The primary endpoint for that study is cardiac safety. Adjuvant bevacizumab hinges on the demonstration of safety because many of these patients will be cured of their disease.

Clinicians will be loath to put patients through anything that might substantially increase their risks of complications. So we'll have to wait and see what that data set looks like and what our Phase II metastatic bevacizumab/trastuzumab combination looks like before we can sign the next adjuvant trial that might incorporate both.

Practicing clinicians should probably wait on the sidelines to see these safety data sets before embarking on any of these combinations. Serious concern for safety exists with these types of combinations, and clinicians shouldn't do anything off protocol in the absence of the Phase II data. ■

— **Mark D Pegram, MD**

► It's certainly possible that adding bevacizumab to an anthracycline might improve the antitumor effect. Most of us believe that bevacizumab is a drug that's acting pretty specifically on the VEGF target, more specifically than the small molecules, like sunitinib, which have multiple targets.

Certainly VEGF is playing a role as a component of a survival signal that allows cells to survive a variety of drugs, including the anthracyclines.

I believe the strongest rationale for potential synergy is emphasized when you're administering a chemotherapy program, either weekly paclitaxel or our so-called metronomic version of AC, for which you have reason to believe that the

program itself is anti-angiogenic, because then you would expect to have a second hit on the same pathway through a different mechanism of action. ■

— Robert B Livingston, MD

► Certainly, concern remains about long-term toxicity associated with bevacizumab. For that matter, some concern exists about short-term toxicity. So within the cooperative groups, the sense is “to wade in” but wade in not so rapidly. A large ECOG pilot trial is evaluating bevacizumab administered in addition to AC → T, primarily with toxicity endpoints in the adjuvant setting. Assuming that pilot study is successful — meaning that it does not show undue toxicity — a large, randomized trial will compare AC → T to AC → T with bevacizumab.

What remains unclear is the timing of the bevacizumab — whether it will be administered with all of the chemotherapy or just with the taxane.

One important aspect of the trial is that not everyone will be assigned to the same duration of bevacizumab. Given concerns about toxicity and about cost issues, an arm of the trial will receive a relatively short duration of bevacizumab.

Finally, a plan is also in place to evaluate bevacizumab within the cooperative groups in the preoperative setting to see if we can better characterize which patients and which tumors derive benefit, because, although we've been unsuccessful in the past with the ability to biopsy and rebiopsy, in the preoperative setting that may be more feasible. ■

— Eric P Winer, MD

SUPPORTING PROTOCOL INFORMATION

The optimal scheduling for administration of doxorubicin and cyclophosphamide followed by paclitaxel (AC → T) was investigated in CALGB-9741. This trial enrolled 2,005 patients in a 2 x 2 factorial design to compare sequential versus concurrent administration of doxorubicin and cyclophosphamide and two 21 day versus 14 day treatment intervals.

Though there was no difference in event rates between sequential and concurrent administration of doxorubicin and cyclophosphamide ($p = 0.67$), use of the 14 day (dose dense) schedule improved both disease-free and overall survival ($p = 0.013$).

The improvement in overall survival with the dose dense schedule persisted in a multivariate Cox proportional hazards model after adjusting for standard baseline covariates (risk ratio 1.45; $p = 0.014$). ...

Over the last two decades substantial laboratory and indirect clinical evidence has accumulated to support the central role of angiogenesis in breast cancer progression. This nascent vascular network provides a novel opportunity for therapy. However, as tumors progress, increasing numbers of pro-angiogenic peptides are produced.

As such, the most successful clinical applica-

tion of angiogenesis inhibitors is likely to be in the adjuvant setting. ...Proof of this concept will require large, prospective randomized trials in the adjuvant setting.

This trial will provide the safety and feasibility data in a selected group of patients with early stage disease needed to justify a full-scale phase III adjuvant trial. ...

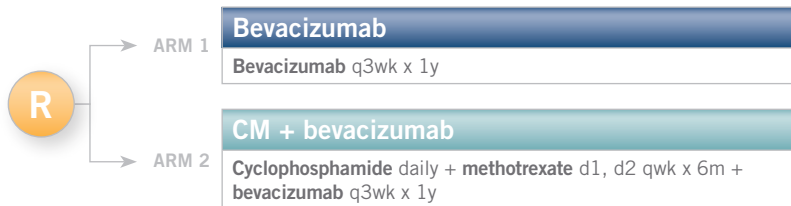
Bevacizumab has been studied in at least 3,500 patients in a number of Phase I, II, and III clinical trials in a number of tumor types, including colorectal, breast, lung, and renal carcinoma. In the Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage.

Completed Phase II and Phase III studies of bevacizumab have further defined the safety profile of this agent in patients with metastatic malignancies.

Also during the Phase III trials, three new possible bevacizumab-associated safety signals were identified: congestive heart failure (CHF) in patients who had been exposed to anthracyclines, gastrointestinal perforations, and wound healing complications.

Trial NCT00121134

A Phase II pilot study of bevacizumab with or without cyclophosphamide and methotrexate in patients with residual tumor after preoperative chemotherapy

TRIAL DESIGN**KEY FACTS****Select Eligibility Criteria**

- Invasive breast cancer, preoperative AJCC Stage II-III based on baseline clinical examination and/or breast imaging
- Completion of any standard preoperative chemotherapy regimen
- Primary tumor resection with adequate excision
- Significant residual invasive disease after surgery
- Initiation of therapy after XRT (if administered) and concurrently with endocrine or anti-HER2 therapy (if administered)
- No history of thromboembolic disease, including DVT/PE, TIA, CVA, unstable angina or MI within the last six months, or clinically significant peripheral arterial disease
- No history of bleeding diathesis or coagulopathy

- No history of abdominal fistula, GI perforation, intra-abdominal abscess or serious nonhealing wound, ulcer or bone fracture within the last six months

Primary Endpoints

- Feasibility of bevacizumab with or without metronomic chemotherapy for breast cancer treatment, toxicity

Secondary Endpoints

- Rate and predictors of recurrent disease, correlative markers, quality of life

Target Accrual: 100

Date Activated: June 2005

Study Contact

*Dana-Farber/Harvard Cancer Center at Dana-Farber Cancer Institute
Beth Israel Deaconess Medical Center
Harold Burstein, MD, PhD, Principal Investigator*

SOURCES: Harold Burstein, MD, PhD. Personal communication; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► The study that we have activated now at Dana-Farber and Indiana University with my good friends Kathy Miller and George Sledge is a pilot study of bevacizumab in the adjuvant setting. The patient population has had preoperative chemotherapy for breast cancer and has residual cancer at the time of their surgery.

Those patients will be offered one year of bevacizumab therapy to see if it's feasible, and then

a second cohort of the same type of patients will be offered one year of bevacizumab and six months of metronomic chemotherapy.

We chose this patient population for a couple of specific reasons. First, we know that women who have residual disease after preoperative chemotherapy constitute a patient population at high risk, for whom there is no standard treatment.

Second, these women have tumors that by defini-

tion have some resistance to chemotherapy. So instead of just treating them with more chemotherapy, we thought it would be interesting to bring in a biologic agent.

When we find residual disease after neoadjuvant chemotherapy, clinicians are tempted to offer more chemotherapy, which is understandable. However, there are many reasons to believe it's not going to be effective.

First, no data suggest that more chemotherapy is beneficial in this setting. Second, there's reason to believe that women with tumors like that have disease that is more or less intrinsically resistant to chemotherapy.

The rationale for the bevacizumab-alone arm was also twofold. First, we don't know that bevacizumab alone would not be effective.

Of course, the adjuvant trials that are going to answer this question will ultimately be large cooperative group studies of chemotherapy with or without bevacizumab.

Second, we wanted to see if it would be safe to give six to 12 months of bevacizumab in the adjuvant setting. Bevacizumab alone has the advantage of being better tolerated, so when you start discussing extended periods of therapy, it probably is more feasible.

We also have some handsome correlative studies built into this trial. These studies take advantage of the proteomics research for which Indiana University is well known and evaluate some other markers of tumor recurrence and endothelial cell biology in which our group is interested. ■

— **Harold J Burstein, MD, PhD**

▶ The use of antiangiogenics as adjuvant therapy has its own potential barriers. The toxicity of chronic antiangiogenic therapy remains largely unexplored, as is the toxicity of combinations of chemotherapy with antiangiogenic therapy.

Although intuitively the impact of angiogenesis inhibition is expected to be greatest in patients with micrometastatic disease, proof of this concept will require commitment of substantial human and financial resources to a randomized adjuvant trial. ■

— **Bryan P Schneider, MD, Kathy D Miller, MD.**
J Clin Oncol 2005;23(8):1782-90.

▶ Conventional cytotoxic chemotherapeutic drugs treat cancer either by direct killing or by inhibi-

tion of growth of cycling tumor cells. In addition, evidence suggests that cytotoxic agents may inhibit tumor growth through an antiangiogenic mechanism.

“Metronomic” or frequent continuous administration of the same chemotherapeutic agents at lower doses may optimize their antiangiogenic properties.

The effectiveness of metronomic chemotherapy regimens can be improved significantly by concurrent administration of antiangiogenic, endothelial-specific drugs.

Preclinical studies have shown that integrating chemotherapy with antiangiogenic drugs can improve efficacy and circumvent the toxicity and drug resistance associated with standard or high-dose chemotherapy.

Preliminary clinical studies have shown similar results. ■

— **Harman P Kaur, MD, Thomas G Budd, MD.**
Curr Oncol Rep 2004;6(1):49-52.

▶ An intriguing hypothesis is the possibility of synergy between anti-VEGF agents and chemotherapy, with respect to the inhibition of angiogenesis.

Chemotherapy likely targets dividing endothelial cells found in newly forming blood vessels; however, these cells are relatively slow growing, and conventional cycle lengths may allow for repair and recovery from some of the chemotherapy-induced damage.

Researchers have devised antiangiogenic or metronomic chemotherapy dosing schedules in order to apply continuous pressure on the newly forming tumor vasculature and possibly overcome acquired chemotherapy resistance.

This approach involves either continuous chemotherapy infusion or regular, frequent chemotherapy administration, generally with lower chemotherapy doses to avoid excess toxicity.

Indeed, there is evidence in humans that this approach overcomes drug resistance, as patients resistant to conventional taxane therapy have been found to respond subsequently to lower-dose weekly treatment. ■

— **Clifford Hudis, MD.**
Oncology (Williston Park) 2005;
19(4 Suppl 3):26-31.

SoFEA

A study of fulvestrant with versus without anastrozole versus exemestane after relapse or progression on nonsteroidal aromatase inhibitors

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Locally advanced/metastatic breast cancer that progressed after treatment with a nonsteroidal aromatase inhibitor
- ER-positive and/or PR-positive

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Objective tumor response rate (CR + PR)
- Duration of objective tumor response
- Clinical benefit rate
- Duration of clinical benefit
- Time to treatment failure
- Overall survival
- In the event that the primary endpoint analysis of fulvestrant versus fulvestrant with anastrozole shows equivalence, a

secondary analysis comparing the progression-free survival of all fulvestrant-treated patients with that of exemestane-treated patients will be performed.

Primary Hypothesis

Cancer cells may be hypersensitive to E2, so it is hypothesized that fulvestrant could be more effective in an environment of continued “low” compared with “normal physiological” postmenopausal E2 levels.

Target Accrual: 750

Date Activated: March 1, 2004

Study Contact

Institute of Cancer Research — Sutton
Stephen Johnston, MD, PhD, FRCP,
Protocol Chair

SOURCES: SoFEA Protocol, August 2, 2004; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► The SoFEA trial is evaluating the use of endocrine therapy in the metastatic disease setting, comparing exemestane as a single agent to fulvestrant to the combination of anastrozole and fulvestrant.

The combined therapy arm may be the most interesting one. The rationale behind it is not only removing the ligand for the receptor — which

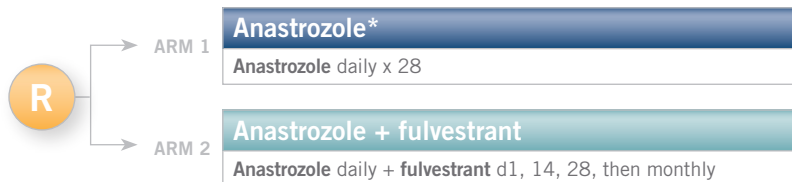
is what the aromatase inhibitor would do by decreasing the amount of circulating estrogen — but also eradicating the actual target, which is the receptor. Answering whether absolute removal of those two targets will result in a better outcome is one of the goals of the study. ■

— William J Gradishar, MD

SWOG-S0226

A Phase III randomized study of anastrozole with or without fulvestrant as first-line therapy

TRIAL DESIGN



* Crossover to fulvestrant on progression or symptomatic deterioration

KEY FACTS

Stratification

- Prior adjuvant tamoxifen

Primary Endpoint

- Time to progression

Secondary Endpoints

- Clinical response rate, overall survival

Target Accrual: 690 within 3 years

Current Accrual: 198 (9/29/06)

Date Activated: April 1, 2004

Study Contacts

Southwest Oncology Group

Rita Mehta, MD, Study Coordinator

NCIC-Clinical Trials Group

Theodore Vandenberg, MD, Protocol Chair

SOURCES: SWOG S0226 Protocol, July 2006; swog.org.

► In the clinical setting, I think it is a good idea for patients who are progressing on aromatase inhibitors to continue with an aromatase inhibitor and add fulvestrant, but there are no data. I have done this with a few patients based on two preclinical studies that have evaluated this: my own and Angela Brody's.

Fulvestrant seems to work much better when there's no estrogen around. Even though postmenopausal women have lower estrogen levels in the blood, their tumors don't necessarily have lower estrogen levels, and fulvestrant seems to be more effective when estrogen is low. ■

— C Kent Osborne, MD

► SWOG-S0226 is a randomized, first-line metastatic study in which all patients receive an aromatase inhibitor, and half of them will receive fulvestrant concurrently.

The group that is randomly assigned to receive the aromatase inhibitor alone is then asked to switch to fulvestrant at the time of progression,

although we know we can't force their next-line therapy.

So it's really a question of an up-front aromatase inhibitor with a selective estrogen receptor downregulator (SERD), fulvestrant, versus an aromatase inhibitor followed by the SERD.

We're hoping that we'll obtain complete estrogen blockade by using this regimen. We know that in the ATAC trial, the anastrozole/tamoxifen combination arm did not appear to be any better than tamoxifen alone and certainly wasn't going to be the superior arm.

Tamoxifen can have some proestrogenic properties in an otherwise depleted estrogen state. Fulvestrant shouldn't have these.

It's a pure antiestrogen and thus is an interesting concept that is different from considering an aromatase inhibitor with or without tamoxifen.

Certainly, preclinical data suggest that this could work. It makes sense, and we have high hopes that it could be better. ■

— Julie R Gralow, MD

FACT

Anastrozole monotherapy versus maximal estrogen blockade with anastrozole and fulvestrant combination therapy

TRIAL DESIGN



KEY FACTS

Primary Endpoint

- Time to tumor progression

Secondary Endpoints

- Response rate, survival, safety

Target Accrual: 512

Date Activated: January 2004

Select Eligibility Criteria

- Postmenopausal
- Histologically or cytologically confirmed ER-positive and/or PR-positive breast cancer

- Local recurrence or metastasis
- No previous systemic endocrine therapy for advanced or recurrent disease
- No prior fulvestrant therapy

Study Contact

AstraZeneca Pharmaceuticals LP
Roger Henriksson, MD, Study Director

SOURCES: NCI Physician Data Query, October 2006; clinicaltrials.gov, October 2006.

► In patients progressing on tamoxifen, tamoxifen binds the estrogen receptors and may actually stimulate growth of the tumor — it certainly is no longer inhibiting it. Treating these patients with an aromatase inhibitor will be ineffective until all the tamoxifen is gone, which takes a couple of months.

Fulvestrant, on the other hand, competes with tamoxifen for binding, thus the response may be quicker with fulvestrant than with an aromatase inhibitor in that setting. ■

— C Kent Osborne, MD

► In cell culture, when MCF7 cells are depleted of estradiol, they become extremely sensitive to low levels of estrogen. The cell line can be inhibited if fulvestrant is then titrated into that long-term estrogen-deprived cell line.

The rationale behind the SoFEA study is that the development of resistance to aromatase inhibitors may result from an increased sensitivity of breast cancer cells to very low levels of estradiol.

Fulvestrant competes with estradiol for the estrogen receptor on a one-to-one basis so that upon progression while on the aromatase inhibitor, the addition of fulvestrant to the aromatase inhibitor might result in a better blocking effect.

I hope the SoFEA trial will show that there is improvement from the combination of fulvestrant and an aromatase inhibitor.

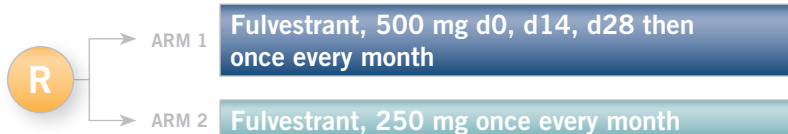
This will be an interesting study, not only because it will tell us what to do in second- or third-line therapy but because it will also tell us about mechanisms of action and whether they are important in breast cancer. ■

— John F R Robertson, MD

CONFIRM trial

A Phase III randomized trial of fulvestrant at 500 mg versus fulvestrant at 250 mg for postmenopausal women with ER-positive advanced breast cancer progressing or relapsing after previous endocrine therapy

TRIAL DESIGN



KEY FACTS

Primary Endpoint

- Time to progression

Secondary Endpoints

- Objective response, clinical benefit rate, duration of response, duration of clinical benefit, overall survival, quality of life

Target Accrual: 720

Date Activated: August 2005

Study Contact

AstraZeneca Pharmaceuticals LP
AstraZeneca Cancer Support Network

SOURCES: 'Faslodex' Ongoing Clinical Studies Clinical Trial Booklet, August 2005. AstraZeneca Oncology; faslodex.net.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► An important issue is whether fulvestrant at 250 mg is optimal, even though that's the approved dose. Some of the data, including preclinical data generated by Kent Osborne and others, suggest that this dose is on the low end of the curve where you might expect the optimal response rate.

Although we may be able to increase the dose, administering 250 mg in each buttock, doing that too frequently becomes prohibitive, and patients may not tolerate it.

Some strategies have evaluated quickly increasing serum levels of fulvestrant, and those strategies have included administering loading doses of 500 mg and then, within two weeks, administering another 250 mg and then proceeding to the monthly schedule.

Those strategies are based on mathematical modeling that have shown an ability to achieve steady-state levels much quicker and, conse-

quently, achieve a biologically relevant dose of drug circulating in a given patient much faster. ■

— William J Gradishar, MD

► We expected fulvestrant to be superior to tamoxifen, but in the first-line setting it proved to be similar, not better.

That's peculiar because second-line trials show fulvestrant to be equal to or better than aromatase inhibitors, and aromatase inhibitors have been shown to be superior to tamoxifen.

It may be that we're just not dosing fulvestrant correctly. We know from the randomized trial that half of the currently recommended dose is insufficient, and we know it takes three to six treatments to achieve steady state blood levels with fulvestrant, so perhaps a higher dose or a loading dose (or both) is required. These options are being investigated. ■

— C Kent Osborne, MD

► Fulvestrant at 250 mg is an effective dose, as demonstrated by the clinical trials. It is as effective as anastrozole as second-line therapy and equivalent to tamoxifen as first-line therapy in postmenopausal women.

In premenopausal women, data suggest that 250 mg of fulvestrant is not effective at downregulating the estrogen receptor.

This raises questions about whether a 250-mg dose of fulvestrant leads to complete downregulation of the estrogen receptor in postmenopausal women. Could a higher dose of fulvestrant achieve more?

Two strategies exist to increase the dose of fulvestrant. The first is a loading dose sequence. The second is the administration of a higher dose of fulvestrant.

For example, instead of administering one 5-mL injection every month in one buttock, one might administer one 5-mL injection in each buttock, for a total of 500 mg. Future studies are needed to determine the dose-response curve for fulvestrant. ■

— **John F R Robertson, MD**

► I believe the trials of fulvestrant underestimate the efficacy of this agent.

The dosing schedule used was probably too low because by the time steady state was reached, many patients were off study, presumably because of progression. In my group, we administer loading doses of 500 mg of fulvestrant, followed by 500 mg two weeks later and then 250 mg monthly.

The pharmacokinetics of fulvestrant suggest a loading dose would be beneficial, so it concerns me that the comparison of fulvestrant to anastrozole in a tamoxifen-resistant population might not have revealed the true efficacy of fulvestrant. It showed fulvestrant to be at least as effective as anastrozole, but I expected it to be superior.

We may need to repeat some of these studies with a more appropriate dosing schedule. ■

— **Gabriel N Hortobagyi, MD**

► An earlier study by John Robertson showed no biological effect when using a standard dose of 250 mg in premenopausal women.

We subsequently performed a study in premenopausal women using a 750-mg dose given in three 250-mg injections, which was remarkably tolerated by patients.

Side effects were all Grade I — some headaches and occasional flushes. No significant reactions occurred at the injection site, and patients had transient discomfort.

We saw much greater activity in the tumor with a 750-mg dose than we did with the 250-mg dose. A significant reduction in proliferation occurred, and as in postmenopausal women at the 250-mg dose, the estrogen and progesterone receptors decreased.

Still, there is a possible need for more than 750 mg, and I am interested in looking at a 1-g loading dose, then 500 mg at regular intervals for it to be effective in premenopausal women. ■

— **Michael J Dixon, MD**

► I am a little disquieted by the fact that it can take three to five months to reach a steady state with fulvestrant. A patient with rapidly progressing disease may not benefit from fulvestrant, but fortunately most women with hormone-responsive breast cancer have relatively indolent disease.

I'm interested in the clinical trial in which they are loading fulvestrant at 500 mg every two weeks for a couple of doses and then reducing it to 250 mg monthly. That makes sense to me. ■

— **Joyce O'Shaughnessy, MD**

► At MD Anderson, we use a loading dose of fulvestrant. We administer 500 mg on day one, 250 mg on day 15 and day 29 and then monthly. Many of the key investigators in the early development of the drug believe it is important to attain steady state, but there are no randomized data for the loading approach.

Currently, it is FDA approved at 250 mg monthly and is reimbursed by Medicare at that dose. With all of those caveats, I believe — and I don't know if this is my bias — the loading approach is reasonable.

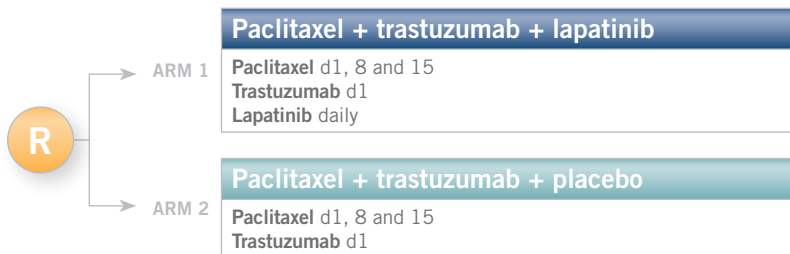
Although we think that may be the best dosing schedule, we won't know unless we do a pharmacokinetic study to show that the doses are equally effective. ■

— **Vicente Valero, MD**

TRIAL DESIGNS

Trial EGF104383

An erbB2-overexpressing metastatic breast cancer study using paclitaxel, trastuzumab and lapatinib



KEY FACTS

Primary Endpoint

- Time to progression

Secondary Endpoints

- Overall response rate, clinical benefit, time to response, duration of response, progression-free survival, overall survival, quality of life, toxicity

Target Accrual: 70

Date Activated: November 2005

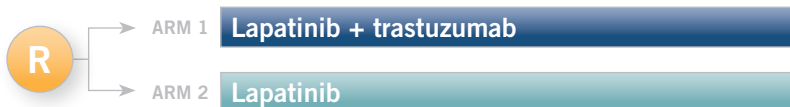
Study Contact

GSK Clinical Trials

SOURCE: clinicaltrials.gov, October 2006.

Trial EGF104900

A Phase III randomized open-label trial of lapatinib in combination with trastuzumab versus lapatinib monotherapy for metastatic breast cancer



KEY FACTS

Select Eligibility Criteria

- Metastatic breast cancer
- FISH-amplified tumors
- Measurable disease defined by RECIST
- Cardiac ejection fraction within institutional normal range
- Prior treatment with taxane, anthracycline and trastuzumab-containing regimen (documented progression must have occurred on trastuzumab-containing regimen)
- No prior therapy with an erbB1 and/or erbB2 inhibitor

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Survival, response rate, clinical benefit, time to response, response duration, quality of life

Protocol IDs: EGF104900, NCT00320385

Target Accrual: 270

Date Activated: November 2005

Study Contact

GSK Clinical Trials

SOURCE: clinicaltrials.gov, October 2006.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► We would like to use drugs that target other aspects of the HER2 pathway. The current leading candidate is lapatinib. It's a dual HER1/HER2 kinase that also inhibits the same target as trastuzumab, actually, HER2, but it inhibits it in a different way. It works on the cytoplasmic kinase domain, which is part of the signaling initiator. Some early data suggest that when you combine lapatinib and trastuzumab, you may get a higher response rate. We know that in early pilot trials, patients who were previously untreated and had HER2-positive disease had good response rates to lapatinib. ■

— **Debu Tripathy, MD**

► Phase I studies of the combination of lapatinib and trastuzumab revealed that at full doses of trastuzumab and full doses up to about 1,500 mg of lapatinib, significant fatigue occurred, so the combination that is tolerable would be with lapatinib at 1,000 mg. This is an active regimen in patients who are candidates for trastuzumab, and it would need to be evaluated.

What I find exciting about the results of the lapatinib/capecitabine study is that there is now a second effective drug to shut down HER2 access, which is the main thing one wants to do when treating patients with HER2-positive breast cancer, because like trastuzumab, it seems that lapatinib allows many chemotherapy drugs to work better. So when there is a second drug that shuts down that access in a different way, the question arises whether there are patients in whom one drug would be better than the other, or where the combination would be better. These are issues that need to be studied in the earlier front line, in neoadjuvant and adjuvant settings. ■

— **Charles E Geyer Jr, MD**

► Trastuzumab and lapatinib work well together, both in vitro and also in clinical trials, in which patients will have had multiple trastuzumab-containing regimens. They have progressive disease, and then the lapatinib is added to the trastuzumab. In that case, response rates in the range of about 27-30 percent are seen. ■

— **Edith A Perez, MD**

► The small-molecule, erbB2 kinase inhibitors are an exciting class of compounds that could be the next to be studied in the adjuvant setting in HER2-positive disease. Specifically, lapatinib seems to be the leader, although it's not a pure HER2 kinase inhibitor because it also inhibits the

EGF receptor kinase. Be that as it may, it has clear activity in HER2-positive metastatic disease, and that's been presented in Phase II cohorts.

We participated in an intriguing study of a combination of trastuzumab and lapatinib, which appears to be promising even in patients with prior treatment failure on trastuzumab. A recent study from South America evaluated single-agent lapatinib in HER2-positive metastatic breast cancer.

Those patients had a response rate of approximately one third, which is similar to what Chuck Vogel presented for single-agent trastuzumab as first-line therapy in patients with HER2-positive metastatic disease, suggesting that lapatinib may have significant activity in this population of patients. So lapatinib is potentially poised to be integrated into the adjuvant setting, either in combination with trastuzumab or following trastuzumab or as a substitute for trastuzumab. ■

— **Mark D Pegram, MD**

► Studies evaluating lapatinib in combination with trastuzumab will be important. Preclinical data suggest there is synergy there. They work by different mechanisms on the HER2 molecule. The next Intergroup adjuvant trial will use an AC → paclitaxel chemotherapy regimen as a backbone. One arm will receive a year of trastuzumab, one arm will receive both added together and the third arm, which is under negotiation, is lapatinib alone without any trastuzumab in the adjuvant setting. Ethically, I believe it's an appropriate arm. We will be reassured by the head-on comparison data of the two drugs in the metastatic setting, and if they are looking fairly equal, it'll be easier to accrue.

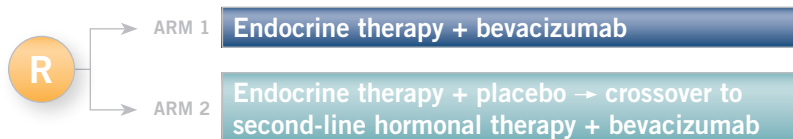
Up-front single-agent lapatinib has been administered to patients who haven't received trastuzumab in other parts of the world, where trastuzumab is not readily available. There are historical controls and you take it with all those caveats, but the response rate and time to progression were virtually identical to those seen when trastuzumab was used as a first-line single agent. Chuck Vogel published that years ago.

So, as a single agent, lapatinib has good activity comparable to that previously seen with trastuzumab. We need the comparison, and it might be that it has to be conducted in other parts of the world. We can't do it here because we have ready access to trastuzumab. ■

— **Julie R Gralow, MD**

CALGB-40503 (proposed)

A Phase III trial of endocrine therapy with or without bevacizumab

TRIAL DESIGN**KEY FACTS****Select Eligibility Criteria**

- Inoperable, locally advanced or metastatic breast cancer
- Postmenopausal (ovarian ablation required if premenopausal)
- No known CNS metastases, recent thromboembolic events, significant proteinuria (>500 mg/24 hr), uncontrolled hypertension, history of DVT or PE, major surgery within the last four weeks or serious non-healing wound or bone fracture
- ER-positive and/or PR-positive
- Measurable or nonmeasurable disease by RECIST
- ECOG PS 0-1

Stratification

- Aromatase inhibitor versus tamoxifen
- Measurable versus nonmeasurable disease
- Premenopausal versus postmenopausal status

Therapy

Endocrine therapy: Physician's choice of aromatase inhibitor or tamoxifen (ovarian suppression required if premenopausal)

Bevacizumab: 15 mg/kg every three weeks

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Progression-free survival at six and 12 months, response rate (measurable disease only), safety (particularly hypertension, proteinuria and thrombosis), duration of response, time to treatment failure, survival at 12 months

Target Accrual: 360 over 18 months

Date Activated: Pending

Study Contacts

Cancer and Leukemia Group B

Maura N Dickler, MD, Principal Investigator

Matthew J Ellis, MD, PhD, Principal Investigator

SOURCE: Maura Dickler, MD. Personal communication.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► Interesting data indicate that estrogen may directly modulate angiogenesis through effects on endothelial cells in both physiologic and pathologic conditions. Interesting data also indicate that antiestrogen therapy blocks VEGF expression, and estrogen-induced angiogenesis may be blocked by anti-estrogen therapy.

Rakesh Jain's group in Boston has observed an androgen-dependent tumor model and shown that castration, interestingly, leads to initial vascular regression, and then there is a second

wave of angiogenesis with vascular regrowth in this murine tumor model.

We participated in a Phase II trial combining letrozole with bevacizumab. The hypothesis was that anti-VEGF therapy may overcome this resistance of the second wave of angiogenesis seen with endocrine therapy in animal models and could improve the efficacy of standard hormone therapy in hormone receptor-positive metastatic breast cancer.

Forty-three patients were enrolled in the trial.

Patients received bevacizumab at 15 mg/kg every three weeks, as well as letrozole at 2.5 milligrams a day. The combination appears to be well tolerated. The drug-related toxicities were expected and only seen in a small number of patients. The efficacy analysis, which wasn't the primary goal of this study, was confounded by the long duration of prestudy aromatase inhibitor therapy most patients received, although it did appear that a number of patients might have benefited from the therapy as a hypothesis.

Principal investigators Maura Dickler and Matt Ellis have planned a Phase III study evaluating patients with hormone-positive disease for first-line therapy. Patients will be randomly assigned to endocrine therapy with placebo or endocrine therapy with bevacizumab. ■

— Hope S Rugo, MD

► Both estrogens and progestins induce VEGF in breast cancer cells through their respective receptors and via characterized hormone response elements. Anti-estrogens and anti-progestins cause some hormone-dependent tumors to regress; however, some tumor cells invariably become resistant to anti-hormones and continue to grow. In certain cases, anti-hormones can even stimulate tumor growth.

It is not known what specifically causes the resistant cells to continue to proliferate, though it has been suggested that growth factors may be involved. Interestingly, clinical studies have shown that tumors with high levels of VEGF fail to respond to hormone therapy or have an early recurrence, suggesting that VEGF production may be responsible for anti-hormone resistance. These studies also re-affirm that VEGF may be responsible for tumor cell proliferation as reported previously. Our recent data indicate that exposure

of breast cancer cells to VEGF can override the effects of anti-hormone, suggesting that a treatment regimen of both anti-hormones and anti-angiogenic agents may be better for tumor suppression than a single regimen alone. ■

— Salman Hyder, PhD. *Endocr Relat Cancer* 2006;13(3):667-97.

► Increased levels of vascular endothelial growth factor (VEGF) are associated with a poor response of breast cancer to anti-hormone treatment. Although VEGF is regarded as an endothelial-specific growth factor, recent reports have shown that VEGF can promote proliferation of other cell types, including breast tumor cells...

VEGF stimulates proliferation of VEGFR2-positive tumor cells, promotes survival via the expression and activity of Bcl-2 and overrides the growth-suppressive effects of anti-hormones. This represents a potential explanation for anti-hormone resistance and tumor progression in clinical samples. Thus, it may be useful to use combined modality treatment involving anti-hormones and anti-angiogenic agents to treat breast cancers that express elevated levels of VEGF. ■

— Yayun Liang, PhD et al. *Endocr Relat Cancer* 2006;13(3):905-19.

► Regulation of soluble VEGFR-1 by estrogen may represent one of the molecular pathways responsible for the angiogenic switch during breast tumorigenesis. Detailed understanding of the role of estrogen and antiestrogens (ie, tamoxifen) used in clinical settings to control VEGFR-1 expression may help in the design of new strategies for preventing resistance to endocrine therapy and may also help clarify the emerging role of estrogen in controlling vascularization. ■

— Michael Elkin, PhD et al. *J Natl Cancer Inst* 2004;96(11):875-8.

SUPPORTING PROTOCOL INFORMATION

Correlative Science Program

- Measurement of baseline and serial levels of CECs and CTCs to explore potential early markers of response or resistance to therapy (Rugo/Park)
- Luminal subtyping by IHC of paraffin-embedded breast tumor tissue to determine any differential response of endocrine therapy + bevacizumab in Luminal A versus Luminal B subtypes (Ellis)

- Assay for genetic variants in VEGF, CYP2D6 (tamoxifen-treated patients) and CYP1A9 (aromatase inhibitor-treated patients) genes to correlate genetic variants with response to Rx
- Serum proteomic analysis to look for biomarkers that may predict resistance to endocrine therapy (Ellis/Townsend)
- Genotyping of phosphoinositol 3 kinase (PIK3CA) from paraffin-embedded tumor tissue (Ellis) to analyze association of PFS with mutated vs nonmutated PIK3CA

UCLA-0502057-01

A Phase II randomized study of fulvestrant and/or trastuzumab as first-line treatment

TRIAL DESIGN



KEY FACTS

Select Eligibility Criteria

- Stage IV disease
- ER-positive and/or PR-positive ($\geq 10\%$ tumor staining or Allred score ≥ 3)
- No prior endocrine therapy, chemotherapy or trastuzumab for metastatic disease
- Postmenopausal
- HER2-positive by FISH

Stratification

- Prior adjuvant endocrine therapy

Primary Endpoint

- Overall objective response rate

Secondary Endpoints

- Duration of response, overall survival, time to disease progression, clinical benefit, safety and toxicity, correlation of HER2 and ER and/or PR expression with response

Target Accrual: 120 (40 per treatment arm)

Date Activated: June 2005

Study Contact

*Jonsson Comprehensive Cancer Center
at UCLA*

Richard Pietras, MD, PhD, Protocol Chair

SOURCES: NCI Physician Data Query, October 2006; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► Combining fulvestrant and trastuzumab makes sense to me, and the reason is that you can see ligand-independent activation of the estrogen receptor in HER2-positive breast cells. That is, the cross talk between HER2 signaling and the estrogen receptor can activate estrogen-dependent genes in the absence of estradiol. What that predicts is that with aromatase inhibitors, you'll have an absence of estradiol and no ligand for the ER, but the ER can still be turned on by HER2 signaling. So that's a kind of strike against aromatase inhibitors. SERMs can actually be more agonistic after this cross talk mechanism.

How can you tackle such a complex issue? One idea would be to get rid of the estrogen receptor, and that's exactly what fulvestrant does. So it is appealing from a theoretical point of view to incorporate HER2-directed therapy with fulvestrant, and we have a randomized Phase II trial under way in the metastatic setting, comparing fulvestrant alone to trastuzumab alone to the combination.

I have a number of patients with ER-positive, HER2-positive disease who are on fulvestrant and trastuzumab and are doing well, though they were started on the treatment off protocol because

the protocol wasn't open when they started, and they're still on it. So I've had some nice anecdotal responders on that combination. ■

— Mark D Pegram, MD

► Our group's main focus is to understand how tumors become resistant to hormone therapy, and others have discovered over the years that there is a relationship between growth factor receptors, such as HER2 and others, and their activities and the estrogen receptor pathway. In a sense, these pathways talk to each other and amplify the signals coming from each. Data from our laboratory studies, now supported by clinical studies, indicate that one of the ways that tumors become resistant to tamoxifen and to estrogen-deprivation therapies such as aromatase inhibitors is from cross talk between growth factor pathways and the estrogen receptor. If that were the case, it would make sense to block both pathways simultaneously in the appropriate tumor to obtain maximum benefit. For instance, if a tumor expresses estrogen receptor and overexpresses HER2, our data suggest that it would be necessary to target both to achieve optimal benefit. Using trastuzumab to block HER2 and leaving the estrogen receptor wide open would not provide very good results, nor would much ground be gained by blocking the estrogen receptor and leaving HER2 wide open, because they cross talk with each other.

Fulvestrant is a purer antagonist of the estrogen receptor and also induces receptor degradation. It behaves much like an aromatase inhibitor. An aromatase inhibitor deprives the estrogen receptor of its activating ligand, estrogen, whereas fulvestrant blocks and eliminates the estrogen receptor. In experimental models, the end result seems to be the same. Therefore, the mechanisms of resistance to one are identical to the mechanisms of resistance to the other.

In our experimental models, in a tumor that is HER2-positive or that acquires increased expression of HER2 or other growth factors with treatment over time, the increasing activity through the HER2 pathway downregulates the estrogen receptor, and the tumor evolves into one that is estrogen receptor-negative. What is happening there is that over time, the increasing HER2 activity downregulates the expression of estrogen receptor and progesterone receptor, via mechanisms described by others, resulting in a tumor that is negative for those receptors. Could you recover estrogen receptor expression if the HER2 pathway is blocked? Or are there patients with

tumors that start out as ER-negative, HER2-positive that could become ER-positive if HER2 is blocked? Now some increasing clinical information is showing that in some patients, the estrogen receptor comes back after HER2 is blocked with trastuzumab or other drugs. This is an interesting new observation both in the laboratory and clinic, and it may be that some of these ER-negative tumors are really not ER-negative. ■

— C Kent Osborne, MD

► Preclinical investigations using in vitro and xenograft models have led to advances in the understanding of the biology of ER and cross-talk with growth factor signal transduction systems. By degrading the ER, fulvestrant may be less likely than tamoxifen to result in the development of endocrine resistance via elevated growth factor signaling cross-talk. Consequently, there is now considerable interest in exploring combinations of fulvestrant with drugs such as trastuzumab, targeted against HER2, gefitinib, targeted against EGFR, and other agents targeted at inhibiting growth factor signaling. Based on the promising activity of these agents in preclinical investigations, several clinical trials have been initiated to assess the effectiveness of such a combination approach in breast cancer therapy. ■

— Mitchell Dowsett et al.

Breast Cancer Res Treat 2005;93:11-18.

► The existence of "cross-talk" between various growth factor receptor signaling pathways and estrogen receptors is now well-established; accumulating evidence suggests that estrogen receptors can become activated and supersensitized by a number of different intracellular kinases, both initially and at the time of relapse. Estrogen receptors remain an integral part of signaling even after failure of aromatase inhibitors or tamoxifen. Therefore, strategies to target the enhanced expression and pathways that activate estrogen receptors need to be explored clinically. Tumor cells are capable of easily bypassing a single agent inhibitor. Consequently, clinical trials combining endocrine therapies and signal transduction inhibitors should be a high priority. Furthermore, targeting multiple vital pathways would theoretically have more antitumor effect and possibly decrease resistance to each individual agent. ■

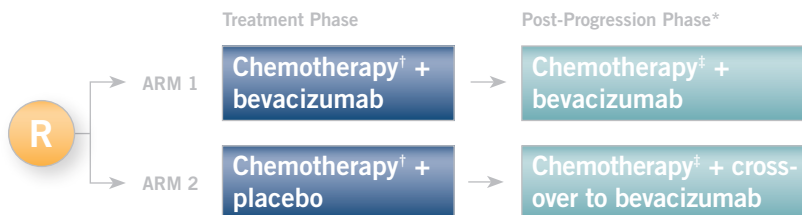
— Zeina A Nahleh, Abdul-Rahman Jazieh.

Am J Clin Oncol 2005;28:631-3.

RIBBON 1 (AVF3694g)

A multicenter, Phase III, randomized, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously untreated metastatic breast cancer

TRIAL DESIGN



Bevacizumab = 15 mg/kg q3wk (or 10 mg/kg q2wk during post progression phase)

* Optional, per investigator's discretion

† Anthracycline-based combination chemotherapy, q3wk taxane (docetaxel or *nab* paclitaxel) or capecitabine, as determined by the investigator prior to randomization

‡ Chemotherapy per investigator's discretion

KEY FACTS

Select Eligibility Criteria

- Metastatic breast cancer
- ECOG PS 0 or 1
- For anthracycline cohort only: LVEF \geq 50% by MUGA or ECHO
- No HER2-positive disease
- No prior chemotherapy for metastatic disease or (neo)adjuvant chemotherapy within the last 12 months
- No NYHA Grade II or greater CHF
- No history of stroke or TIA within the last six months
- No brain or CNS metastases
- No clinically significant peripheral vascular disease
- No evidence of bleeding diathesis or coagulopathy
- No history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within the last six months
- No serious nonhealing wound, ulcer or bone fracture

Stratification

- Disease-free interval
- Prior adjuvant therapy
- Number of metastatic sites
- Choice of chemotherapy

Primary Endpoint

- Progression-free survival (PFS); assessed at first progression

Secondary Endpoints

- PFS in the three primary study cohorts (taxane therapy, anthracycline-based therapy and capecitabine)
- Overall survival and objective response in the primary analysis population
- Best response using RECIST criteria

Target Accrual: 1,050

Date Activated: December 2005

Study Contact

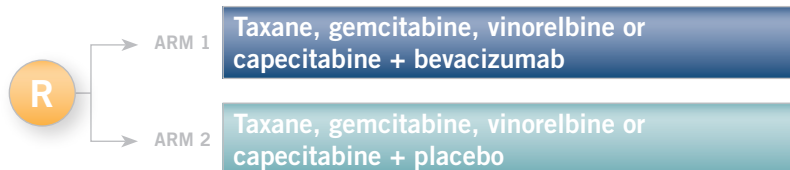
Genentech Incorporated
Barbara J Klencke, MD, Study Director

SOURCES: NCI Physician Data Query, October 2006; Genentech Oncology, Protocol Schema, October 2006; cancer.gov.

RIBBON 2 (AVF3693g)

A Phase III, multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously treated metastatic breast cancer

TRIAL DESIGN



2:1 randomization of Arm 1 to Arm 2

KEY FACTS

Select Eligibility Criteria

- Metastatic breast cancer
- Progression of disease during or following administration of one chemotherapy regimen, defined as a single agent administered prior to disease progression or a prespecified combination or sequence administered in the first-line setting
- ECOG PS 0 or 1
- No unknown or HER2-positive disease
- No unknown ER or PR status
- For those who received prior anthracycline-based therapy: LVEF \geq 50% by MUGA or ECHO
- No NYHA Grade II or greater CHF
- No history of myocardial infarction within the last six months
- No brain or CNS metastases
- No history of stroke or TIA within the last six months
- No clinically significant peripheral vascular disease
- No evidence of bleeding diathesis or coagulopathy
- No history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within the last six months
- No serious nonhealing wound, ulcer or bone fracture
- No major surgical procedure within the last 28 days

Stratification

- Chemotherapy regimen
- Taxane versus capecitabine versus other
- Interval from time of diagnosis
- Metastatic sites: <3 versus >3

Primary Endpoint

- Progression-free survival

Secondary Endpoints

- Overall survival, objective response rate, duration of objective response, safety

Target Accrual: 630

Date Activated: February 2006

Study Contact

Genentech Incorporated
Julie Hambleton, MD, Study Director

SOURCES: NCI Physician Data Query, October 2006; Genentech Oncology, Protocol Schema, October 2006; cancer.gov.

COMMENTS FROM BREAST CANCER INVESTIGATORS

► Bevacizumab is a very exciting agent, and I go countercurrent to some of my colleagues, in that some oncologists take a hard line by saying, "It didn't work with capecitabine and I'm only going to use it in the front line, and I'm not going to use it out back." I've seen a couple of absolutely phenomenal responses in women with

far-advanced disease who have failed many prior forms of chemotherapy.

One woman comes to mind. Her tumor was HER2-positive, and she was already being treated with trastuzumab. We elected to treat her with trastuzumab, *nab* paclitaxel and bevacizumab. She had huge intra-abdominal masses that have

virtually disappeared, and she is able to enjoy her life and her family.

Another young woman was treated with a combination of gemcitabine and bevacizumab and had tumor markers in the many thousands. She had a dramatic antitumor response to the combination, and this is third- or fourth-line therapy.

Within the RIBBON 1 trial, we have the ability to use an anthracycline-based combination, a taxane-based combination or capecitabine, and in keeping with my personal philosophy of trying nonallopurinol regimens, four of the first six patients I put on the study were treated with capecitabine. All four are undergoing some form of antitumor response, objectively and subjectively. Whether they are receiving bevacizumab or not, we don't know. ■

— Charles L Vogel, MD

► I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would now use it in a first-line setting, optimally in combination with paclitaxel as administered in the study. I doubt that the interaction is specific between paclitaxel and bevacizumab, although when administered with capecitabine in more advanced disease, bevacizumab seemed to be less active. That's probably related to the setting rather than the drug. ■

— Eric P Winer, MD

► In ECOG-E2100 the progression-free survivals are now approximately a year for the combination of bevacizumab and paclitaxel. If we saw progression-free survivals in the same ballpark in the XCalibr trial evaluating bevacizumab and capecitabine as first-line therapy, I believe we'd all find that very exciting, and it would certainly suggest that we might be able to combine bevacizumab successfully with other chemotherapeutic agents in a more up-front population.

It becomes important in an era when patients are receiving more and more of their therapy in the adjuvant setting, or more intensive chemotherapy in the adjuvant setting, so that drugs like capecitabine might be a preferential first choice for many patients in the front-line metastatic setting. ■

— George W Sledge Jr, MD

► The bevacizumab story is interesting because, although I focus on breast cancer, it seems to work in almost every tumor type in which it has been studied. It is clearly active in breast cancer. The E2100 study reported by Kathy Miller

demonstrated the same order of benefit that we saw combining trastuzumab with chemotherapy in metastatic disease, and suddenly everyone's excited about moving bevacizumab into the adjuvant setting. Randomized studies are under way evaluating single agents — gemcitabine, docetaxel, doxorubicin, capecitabine and *nab* paclitaxel — with or without bevacizumab to prove efficacy. ■

— Stephen E Jones, MD

► In the metastatic disease trials, the reasons for focusing on progression-free survival rather than response rate or overall survival are complex. First, there is an appreciation that clinical improvement with response is a relatively soft endpoint for most patients. Patients would like to live longer and live free of cancer longer.

Second, a theoretical argument exists that newer drugs that target vasculature might not contribute to response as much as they may simply delay progression. So with some of the drugs that are thought to be inhibitors of tumor differentiation or drugs that might slow down angiogenesis, you might see improvement in progression-free survival without a difference in objective response.

For instance, with bevacizumab in the Phase II trials in renal cell cancer, there were hardly any responses, but we did see a dose-dependent difference in time to progression, even though few patients had objective responses. Interestingly, that has not, as yet, been the case with traditional solid tumors in lung, colon and breast studies. The improvement in progression-free survival has been more or less matched by improvements in response rate. What's lacking in all the bevacizumab studies to date is a predictive marker indicating which patients are likely to benefit and which are not. We don't have a marker like estrogen receptor or HER2 that would identify patients who are more likely to respond. ■

— Harold J Burstein, MD, PhD

► We have observed that in patients with metastatic breast cancer, the absence or continued presence of elevated tumor cells after therapy made an enormous difference in the time to tumor progression. I believe more patients will clear their circulating tumor cells as a consequence of bevacizumab. Several clinical trials of bevacizumab are now including correlative studies of circulating endothelial cells. ■

— Daniel Hayes, MD

EDITOR'S COMMENT: *On the enclosed audio program, breast cancer clinical investigators discuss a number of trials currently under development. Below, find excerpts of these thoughts and several of the trial designs being considered.*

WILL THE ADDITION OF A SECOND TARGETED BIOLOGIC THERAPY TO CHEMOTHERAPY/TRASTUZUMAB IMPROVE ADJUVANT OUTCOMES FOR PATIENTS WITH HER2-POSITIVE TUMORS?

► The NSABP is planning a replacement trial for the NSABP-B-31 study, which will evaluate the addition of bevacizumab to the B-31 regimen of AC followed by paclitaxel/trastuzumab with continued trastuzumab.

We're dealing with the HER2 subset of patients, which is 20 to 25 percent of the total, so it would be foolish to attempt this kind of trial on our own. We would like this to evolve as a global trial, and we've been working toward that end in partnership with the BCIRG so we can have every opportunity to be successful in addressing the endpoints with the appropriate power. The preclinical data of the combination of trastuzumab and bevacizumab are interesting. The clinical data are limited to a small subset, but they are exciting.

Our C-08 trial in colon cancer evaluating FOLFOX and bevacizumab just closed with about 2,600 patients accrued in two years. In that study, we have not observed any unanticipated toxicities with bevacizumab in the adjuvant setting.

The Aphrodite trial (see next page) — although it may not actually be called Aphrodite, so the trial formerly known as Aphrodite — is a formidable clinical trial. I believe it addresses a meaningful concept, which is the comparison of trastuzumab to lapatinib to the combination of trastuzumab and lapatinib to the sequence of trastuzumab followed by lapatinib in the adjuvant setting.

We are developing a neoadjuvant trial for patients

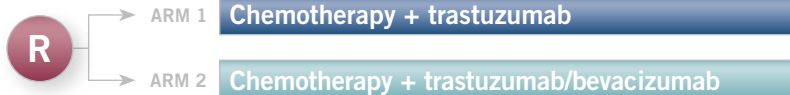
with HER2-positive disease in which we will compare trastuzumab to lapatinib to the combination of trastuzumab and lapatinib.

Not many patients have received the combination of trastuzumab and lapatinib. The last time I examined the available data, for the approximately 110 or 120 patients who have received this doublet, it appears to be safe as far as the cardiac endpoints are concerned. Beyond that, I don't believe we have a whole lot of information. I haven't seen any data that concern me regarding the cardiac effects of lapatinib. I am enthusiastic about the data Chuck Geyer presented at ASCO, and I believe this opens up a new direction for moving forward. However, this needs to be completed in a stepwise, logical way using well-controlled clinical trials. ■

— Norman Wolmark, MD

► The lapatinib data are exciting. Lapatinib is a small-molecule receptor tyrosine kinase inhibitor of HER1 and HER2. We have data from a Phase III trial in refractory metastatic breast cancer that were presented at the 2006 American Society of Clinical Oncology meeting by Chuck Geyer on behalf of an international consortium of colleagues. This trial randomly assigned patients who had disease progression on a trastuzumab-based regimen to receive capecitabine alone, the FDA standard, or capecitabine with lapatinib in this anthracycline/taxane-refractory population.

Proposed NSABP-B-31 replacement trial A Phase III randomized trial of adjuvant therapy for HER2-amplified breast cancer



SOURCE: Norman Wolmark, MD. Personal communication, September 2006.

The results of this trial were strikingly positive in terms of the primary endpoint with, in essence, a doubling of progression-free survival for patients receiving the combination. To date, there's not been an overall survival advantage in that population, and it may require further maturation of the data to see if that advantage will occur.

Lapatinib is an interesting drug. Based on this trial and previous Phase I and Phase II studies conducted at a number of institutions, lapatinib is a legitimate contender in the metastatic and adjuvant settings for further clinical trials trying to push it, if you will, higher up the food chain to try to improve the curability of HER2-positive breast cancer. I view this as an exciting approach. ■

— **George W Sledge Jr, MD**

► The US cooperative groups are undertaking a huge international effort to coordinate the adjuvant trials for patients with HER2-positive disease. We're working with the Europeans, and

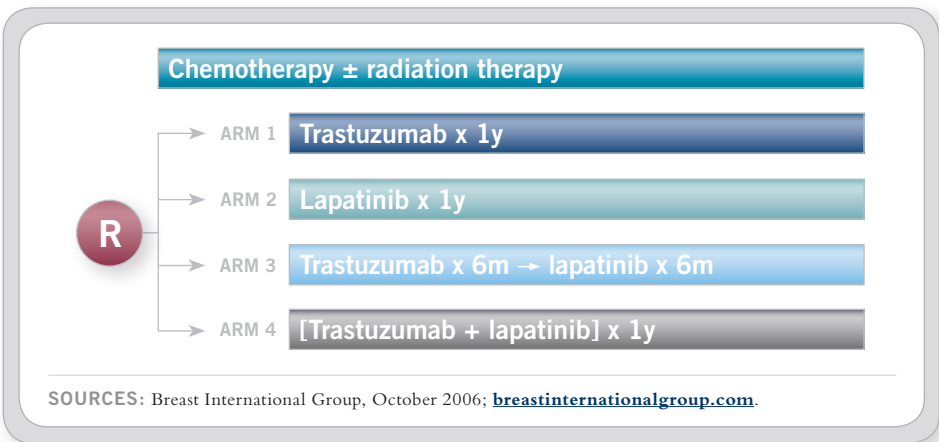
the latest design I saw a week ago, which may already be outdated, has four arms. It has no mandated chemotherapy regimen per se but includes a number of choices, and following the chemotherapy, there will be four arms — a trastuzumab-alone arm, a lapatinib-alone arm and arms that have combinations either in sequence or concurrently.

I don't believe lapatinib will replace trastuzumab because they have different mechanisms. They will not have complete cross-resistance and have potential for synergy, so lapatinib looks like a terrific drug. Edith Perez is the North American representative for this trial, and there are lots of hurdles but the investigators are putting in a lot of effort. We know that we have down time now with no open trial for these patients, so we are hoping to get this study up and going by the first quarter of 2007. ■

— **Julie R Gralow, MD**

BIG 2-06, Aphrodite

Trastuzumab versus lapatinib versus trastuzumab followed by lapatinib versus trastuzumab with lapatinib for postmenopausal patients with ER-positive, PR-positive, HER2-positive breast cancer



HOW CAN NEOADJUVANT TRIALS EXPEDITE THE DEVELOPMENT OF EFFECTIVE SYSTEMIC AGENTS AND REGIMENS?

► Right now, the CALGB is aggressively moving in a new direction. We are developing several clinical trials in the preoperative setting to address the global problem we have, which is to develop drugs in the face of an exciting development — the falling hazard rates in our clinical trials.

For example, my understanding is that the adjuvant trial ECOG-E1199, which compared paclitaxel to docetaxel administered every three weeks versus weekly, never reached its target event number that would have generated its first report. The reasons for that are complex, but

mostly it's just that we're doing better than we ever did before.

Going forward, that low event rate is going to continue to be a challenge for us. For example, among patients with HER2-positive disease being treated with trastuzumab and ER-positive disease being treated over the long haul with hormone therapy, the event rates are going to be even lower than they've been. This doesn't mean that we don't need better therapy — we do — but proving that we have better therapy will require us to focus our efforts.

Our hope is that in-breast activity will serve as a surrogate for overall benefit and give us a lead on how to proceed. So for HER2-positive disease, we're developing a clinical trial testing lapatinib with chemotherapy, and for HER2-normal disease, we're developing a clinical trial testing bevacizumab. We hope to see a lead that one approach is clearly more active in the preoperative setting or that one approach is sometimes associated with specific biological changes that predict lack of benefit. We need to explore these prospectively

before we get to large adjuvant trials. ■

— Clifford Hudis, MD

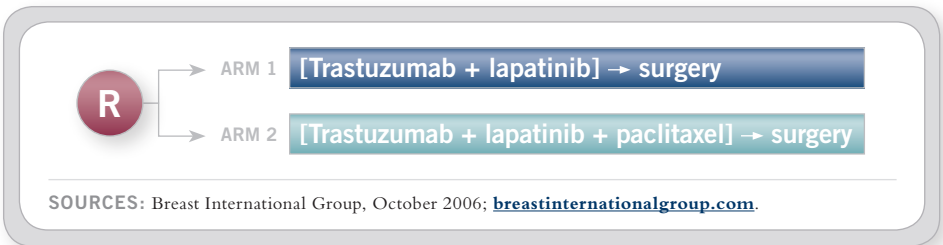
► We previously planned on working with ACOSOG in initiating a neoadjuvant trial for patients with HER2-positive disease that would examine the Buzdar regimen — paclitaxel → FEC with trastuzumab — compared to a more standard trastuzumab-containing regimen in order to confirm the robust pathologic complete response rate reported for that small subset of patients. For various reasons, this trial was not initiated as a partnership between our groups, but I believe ACOSOG will move it forward.

The NSABP is now in the process of developing a neoadjuvant trial for patients with HER2-positive disease, which will compare trastuzumab versus lapatinib versus the combination administered with AC → paclitaxel. The trial will be powered to evaluate pathologic complete response rate and for evolving a molecular taxonomy. ■

— Norman Wolmark, MD

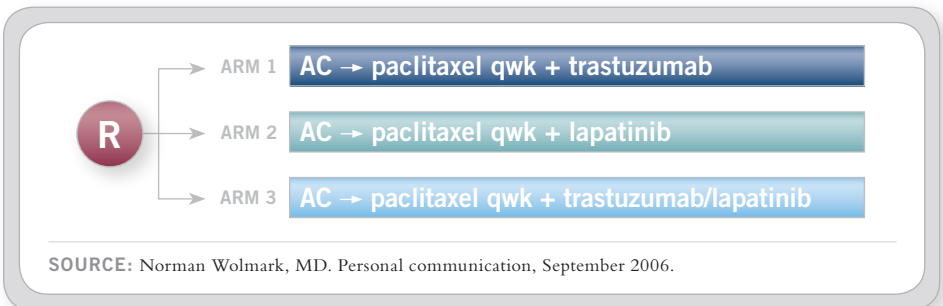
BIG 1-06, NEOAPHRODITE

A Phase III study of neoadjuvant lapatinib and trastuzumab versus lapatinib and trastuzumab with paclitaxel for patients with HER2-positive breast cancer



Proposed NSABP trial

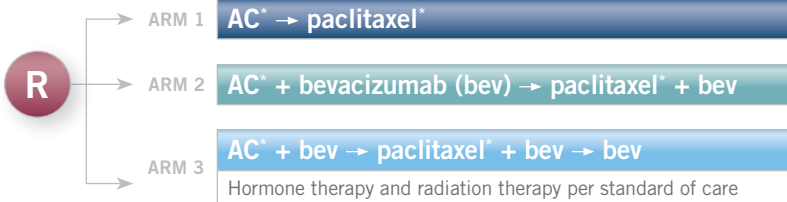
A randomized Phase III trial of neoadjuvant therapy in patients with palpable and operable HER2-overexpressing breast cancer



WILL THE USE OF BEVACIZUMAB IN THE ADJUVANT SETTING IMPROVE THE OUTCOMES OF PATIENTS WITH HER2-NEGATIVE TUMORS?

ECOG-E5103 (pending)

A Phase III adjuvant study of chemotherapy and bevacizumab in patients with HER2-negative, node-positive or high-risk node-negative early breast cancer



* Investigator's choice of classic or dose-dense chemotherapy

SOURCE: George W Sledge, MD. Personal communication, September 2006.

► The Intergroup trial E2100 randomly assigned patients in the front-line setting to receive paclitaxel with or without bevacizumab for the treatment of metastatic breast cancer. The data from that trial, with now increasingly mature follow-up, suggest a striking improvement in progression-free survival for patients who received the combination therapy.

In metastatic breast cancer, this represents the first important proof-of-concept study, suggesting that anti-VEGF targeted therapy in particular and anti-angiogenic therapy in general could have a real benefit for patients with advanced disease.

Now, as always in breast cancer, when we have a positive result for patients who are, in large part, incurable, we like to move that therapy as quickly as possible into a setting where we might be able to improve the curability of the disease. This has led to the development of the Breast Cancer Intergroup trial E5103.

This study will randomly assign patients with lymph node-positive breast cancer to one of three arms. The first arm, the backbone chemotherapy arm, will be doxorubicin and cyclophosphamide followed by paclitaxel.

It is interesting that, to improve accrual in the trial and because many physicians still have biases one way or the other, we are allowing physicians to choose whether patients receive the chemotherapy on a more classic every three-week

basis or on a dose-dense schedule.

Patients in the second and third arms of the trial will receive bevacizumab concurrent with the AC and the paclitaxel. The difference will be the duration of bevacizumab therapy. In the second arm, patients will receive bevacizumab only during the course of chemotherapy, whereas in the third arm patients will continue bevacizumab for a total duration of one year.

The duration question is one that we haven't answered very well with other biologics. Trastuzumab springs to mind as the one where eight or nine years after the drug came on the market, we're still wrestling with how long we should administer it. In the E5103 trial, we'll be able to answer this question from the get-go with bevacizumab in an appropriate adjuvant population.

This study is also interesting from a biological standpoint. We don't have a good sense of the mechanism of action of bevacizumab. If one believes there is synergy between chemotherapeutics and anti-angiogenics against endothelial cells, which preclinical data suggest, or that bevacizumab is altering the ability of chemotherapy to get into a tumor, based on Rakesh Jain's observations, then a great deal of the effect might be a magnifier effect and, therefore, we might see the greatest benefit with a short duration of therapy.

However, it might be that bevacizumab benefits

patients via chronic suppression of new blood vessel formation and, therefore, longer duration might be important. I believe the second and third arms will give us an answer to that important question.

I'm incredibly excited about this trial. I view it as the culmination of a decade's work with anti-angiogenic therapy in breast cancer. If we consider the initial pivotal metastatic trial for trastuzumab in breast cancer and compare it to E2100, with regard to hazard ratios and progression-free survival improvement, E2100 looks as positive as the pivotal trastuzumab trial did a decade ago.

If one can extrapolate from the metastatic setting to the adjuvant setting, then we might see a striking result in the adjuvant setting for a much broader population of patients.

With regard to the issue of arterial events, if one examines all of the metastatic trial data with bevacizumab, one sees a modest increase in these events, which raises concerns for the long-term risk of cerebrovascular events and myocardial infarction. However, I suspect that in an adjuvant setting this would be less of a problem. Adjuvant patients are, on average, perhaps a half decade younger than our patients with metastatic disease, and they tend to have fewer comorbidities.

We're more aware of the potential for toxicities such as hypertension and I suspect we'll be increasingly better at controlling those, so I'm cautiously hopeful that this will not be a big issue down the road. ■

— George W Sledge Jr, MD

HOW CAN THE BENEFITS OF ENDOCRINE THERAPY BE IMPROVED BY EXPLOITING GROWTH FACTOR RECEPTOR-ESTROGEN RECEPTOR CROSS-TALK?

► Hal Burstein has a clinical trial that's just opening evaluating fulvestrant with lapatinib. It's not restricted to HER2-positive disease because there are reasons to argue that HER1 and HER2 inhibition will be additive to fulvestrant.

The CALGB is also considering a series of EGFR inhibitors in collaboration with investigators around the United States. As part of that effort, we have begun to evaluate, in collaboration with John Park and Hope Rugo at UCSF, the predictive value of both circulating tumor cells and circulating endothelial cells. From that collaboration in particular, we have the clinical trial that proved the safety of combining bevacizumab with letrozole, and that has led to a randomized trial in the CALGB. Preclinical evidence argues that profound estrogen deprivation may have an anti-angiogenic effect and that bevacizumab could add to that. ■

— Clifford Hudis, MD

► I am the principal investigator for a study that the CALGB has just activated for patients with hormone receptor-positive breast cancer whose tumors have some degree of HER2 overexpression — 1+, 2+ or 3+ by IHC but FISH-negative, and they will be randomly assigned to fulvestrant alone versus fulvestrant with the dual kinase inhibitor lapatinib as treatment for metastatic breast cancer. The question we are asking is whether or not inhibition of EGFR and HER2 can

potentiate the effects of antiestrogen therapy. Many laboratory models — most notably those of Kent Osborne at Baylor — have suggested that if you interfere with the two pathways at once, you can make the antiestrogen effect more potent.

We are going to critically evaluate that in the CALGB. We lowered the bar for HER2 expression, compared to just the strongly positives, for three reasons. One is that for patients who have aromatase inhibitor resistance, which is what is expected in this trial, there is some suggestion that you might get upregulation of HER2. The other is that the threshold for HER2 expression for a benefit from lapatinib has not yet been established, and the third is that because lapatinib has this EGFR inhibition potential, we wanted to see if some of that might also be in play. So that study is being activated around the country, and I hope it will accrue handsomely. ■

— Harold J Burstein, MD, PhD

► Our group's main focus is to understand how tumors become resistant to hormone therapy, and what we've discovered over the years — as well as others — is the relationship between growth factor receptors such as HER2 and the estrogen receptor pathway. In a sense, these pathways "talk" to each other and amplify the signals from each of the different receptors.

We have data from our laboratory studies — that are beginning to be supported by results

from clinical trials — indicating that one of the ways tumors can become resistant to endocrine therapies like tamoxifen and aromatase inhibitors is through cross-talk between growth factor pathways and the estrogen receptor pathway. If that is the case, then it makes sense to try to block multiple pathways simultaneously in the appropriate tumor to achieve maximum benefit. If a tumor that expresses the estrogen receptor also overexpresses HER2, our data suggest that in order to obtain the optimal benefit from those therapies, you need to target both receptors by combining targeted therapies. ■

— C Kent Osborne, MD

► We're now learning that if you shut down one growth factor receptor pathway, you may be upregulating another, and that we should be

thinking about multiple-pathway blockades. One of the more fascinating papers I've seen recently was on lapatinib and was published in the *Proceedings of the National Academy of Sciences* by Neil Spector's group. It showed that if you treated a HER2-positive, ER-positive cell line with lapatinib, fairly quickly you got upregulation of the estrogen receptor.

So tumors like to grow, and if they have multiple pathways, we probably need to shut down multiple pathways rather than assuming that in a HER2-positive tumor we only need to target HER2 or in an estrogen receptor-positive tumor we only need to target the estrogen receptor. It's pretty clear to me that we will need to treat multiple growth factor pathways. ■

— George W Sledge Jr, MD

HOW CAN GENOMIC MARKERS BE BETTER USED AS PREDICTORS OF RESPONSE TO CHEMOTHERAPY?

► The concept of trying to individualize the treatment of cancer is certainly not new, and it's something we are all looking forward to. It seems clear that if you consider where we are in cancer care that diagnostics are going to be the key to unlocking not only more effective use of our current therapies but also acceleration of the development of new therapies.

I think the light bulb went on for everyone with the story of trastuzumab. There is no doubt that, if we had conducted those pivotal trials without a molecular diagnostic test, trastuzumab would have failed. And so, with the advancement of that technology — the ability to look at one gene at a time — it is now possible to look at many genes at once. Clearly, in order to better treat cancer, we need to know cancer. Gene expression profiling with quality technology, rigor and discipline is now allowing us to see cancer and treat it differently.

The *OncoType DX™* assay is currently appropriate for women with node-negative, estrogen receptor-positive tumors. What about node-positive breast cancer? What about women who have micrometastases? What about estrogen receptor-negative breast cancer? If we think about early breast cancer, what about investigating even earlier in the pathogenesis of the disease? What about DCIS? Can we individualize treatment of DCIS? All of these are exciting questions that we hope to answer. ■

— Steven Shak, MD

► The MINDACT (Microarray In Node-negative Disease may Avoid ChemoTherapy) trial will be performed predominantly in Europe, and will be led by the Breast International Group in collaboration with the EORTC and, like TAILORx, will also target women who have lymph node-negative disease. However, it will also allow women who have estrogen receptor-negative disease and HER2-positive disease, which TAILORx does not. The assay they'll be using is the Amsterdam 70-gene profile, which is commercially available under the name Mammoprint™ and requires collection of a fresh frozen tissue specimen. The trial design also differs from TAILORx in that the patient's risk of recurrence will also be estimated by Adjuvant! Online.

The 55 percent or so of the patients who are determined by the Mammoprint assay and the clinical criteria — as estimated by Adjuvant! Online — to be at high risk will receive chemotherapy. The 15 percent of patients who are at low risk by both Mammoprint and clinical criteria will receive endocrine therapy alone. The remainder of the patients, for whom there is discordance between the clinical and genomic criteria — which is estimated to be about 35 percent of all patients — will be randomly assigned to treatment by clinical criteria or treatment by genomic criteria. ■

— Joseph Sparano, MD



Study Contacts

Neoadjuvant Therapy

ACOSOG-Z1031

American College of Surgeons Oncology Group

Matthew Ellis MD, PhD, FRCP, Protocol Chair
Tel: 314-362-8866

American College of Surgeons Oncology Group

John Olson, MD, PhD, Protocol Co-chair
Tel: 919-684-6523
Email: jaomd@duke.edu

Cancer and Leukemia Group B

Kevin Hughes, MD, FACS, Principal Investigator
Tel: 617-724-4800
Email: kshughes@partners.org

NSABP-B-40

National Surgical Adjuvant Breast and Bowel Project

Patient Entry Coordinator
Tel: 412-383-4900

Radiation Therapy

NSABP-B-39

National Surgical Adjuvant Breast and Bowel Project

Frank Vicini, MD, FACR, Protocol Chair
Tel: 248-551-1219; 800-633-7377

Douglas Arthur, MD, Protocol Co-chair
Tel: 804-828-7232
Email: darthur@mcvh-vcu.edu

Robert Kuske, MD, Protocol Co-chair
Tel: 608-263-8500; 800-622-8922
Email: kuske@mail.humonc.wisc.edu

Radiation Therapy Oncology Group

Julia White, MD, Protocol Chair
Tel: 414-805-4462
Email: jwhite@radonc.mcw.edu

Rachel Rabinovitch, MD, Protocol Co-chair
Tel: 720-848-0116; 800-473-2288
Email: rachel.rabinovitch@uchsc.edu

Southwest Oncology Group

Lori Pierce, MD, Protocol Chair
Tel: 734-936-7810; 800-865-1125

Adjuvant Endocrine Therapy

IBIS-II, IBIS-IIB (DCIS)

Cancer Research UK at Imperial College School of Medicine — London

Jack Cuzick, PhD, Study Coordinator
Tel: 44-20-7269-3006

International Breast Cancer Study Group

Katharina Buser, MD, Protocol Chair
Tel: 41-31-309-9501
Email: kbuser@sonnenhof.ch

NSABP-B-42

National Surgical Adjuvant Breast and Bowel Project

Eleftherios Mamounas, MD, MPH, FACS
Protocol Chair
Tel: 412-330-4600; 330-438-6281
Email: tmamounas@aaultman.com

CAN-NCIC-MA27/CFEM345D2411

Novartis Pharmaceuticals Corporation
Novartis Study Chair
Tel: 41-61-324-1111

NCIC-Clinical Trials Group

Paul Goss, MD, PhD, Protocol Chair
Tel: 617-724-3118; 877-726-5130

North Central Cancer Treatment Group

James Ingle, MD, Protocol Chair
Tel: 507-284-8432
Email: ingle.james@mayo.edu

Cancer and Leukemia Group B

Matthew Ellis, MD, PhD, FRCP Protocol Chair
Tel: 314-362-8903; 800-600-3606

Eastern Cooperative Oncology Group

George Sledge, MD, Protocol Chair
Tel: 317-274-0920; 888-600-4822
Email: gsledge@iupui.edu

Southwest Oncology Group

George Budd, MD, Protocol Chair
Tel: 216-444-6480; 800-862-7798

International Breast Cancer Study Group

Manuela Rabaglio, MD, Principal Investigator
Tel: 41-31-632-4370
Email: manuela.rabaglio@insel.ch

SOFT/TEXT/PERCHE

International Breast Cancer Study Group

Prudence Francis, MD, Protocol Chair
Tel: 61-39-656-1701
Email: Prue.Francis@petermac.org

Breast International Group

Prudence Francis, MD, Protocol Chair
Tel: 61-39-656-1701
Email: Prue.Francis@petermac.org

Cancer and Leukemia Group B

Gini Fleming, MD, Protocol Chair
Tel: 773-702-6712; 888-824-0200
Email: gffleming@medicine.bsd.uchicago.edu

TEXT

International Breast Cancer Study Group

Olivia Pagani, MD, Protocol Chair
Tel: 41-91-811-3667

Breast International Group

Olivia Pagani, MD, Protocol Chair
Tel: 41-91-811-3667

Prudence Francis, MD, Protocol Chair
Tel: 61-39-656-1701

PERCHE

International Breast Cancer Study Group

Rosalba Torrissi, MD, Protocol Chair
Tel: 39-02-5748-9482

Breast International Group

Rosalba Torrissi, MD, Protocol Chair
Tel: 39-02-5748-9482

Adjuvant Chemotherapy

SWOG-S0307

Southwest Oncology Group

Julie Gralow, MD, Study Coordinator
Tel: 507-284-2511
Email: pink@u.washington.edu

Robert Livingston, MD, Study Coordinator
Tel: 206-288-1085

North Central Cancer Treatment Group

James Ingle, MD, Study Coordinator
Tel: 507-284-2511
Email: ingle.james@mayo.edu

Eastern Cooperative Oncology Group

Carla Falkson, MD, Study Coordinator
Tel: 205-975-2691
Email: cfalkson@uab.edu

**National Surgical Adjuvant Breast
and Bowel Project**

Alexander Paterson, MD, FRCP, FACP, MBChB,
Study Coordinator
Tel: 403-521-3688
Email: alexpate@cancerboard.ab.ca

Cancer and Leukemia Group B

Elizabeth Dees, MD, Study Coordinator
Tel: 919-843-7714

NCIC-Clinical Trials Group

Mark Clemons, MD, Study Coordinator
Tel: 416-480-5847
Email: mark.clemons@sw.ca

TAILORx

Eastern Cooperative Oncology Group

Joseph Sparano, MD, Protocol Chair
Tel: 718-920-4826
Email: jsparano@montefiore.org

Southwest Oncology Group

Daniel Hayes, MD, Protocol Chair
Tel: 734-615-6725; 800-865-1125
Email: hayesdf@umich.edu

Cancer and Leukemia Group B

Elizabeth Dees, MD, Protocol Chair
Tel: 919-966-4431

American College of Surgeons Oncology Group

John Olson, MD, PhD, Protocol Chair
Tel: 919-668-1767; 888-275-3853
Email: jaomd@duke.edu

North Central Cancer Treatment Group

Edith Perez, MD, Protocol Chair
Tel: 904-953-7283
Email: perez.edith@mayo.edu

NCIC Clinical Trials Group

Kathleen Pritchard, MD, Protocol Chair
Tel: 416-480-4616
Email: kathy.pritchard@sw.ca

**National Surgical Adjuvant Breast
and Bowel Project**

Charles Geyer, FACP, MD, Protocol Chair
Tel: 412-359-8353; 866-680-0004

CALGB-49907

Eastern Cooperative Oncology Group

Hyman Muss, MD, Protocol Chair
Tel: 802-847-3827; 800-358-1144

Eastern Cooperative Oncology Group

Antonio Wolff, MD, Protocol Chair
Tel: 410-614-4192
Email: awolff@jhmi.edu

Southwest Oncology Group

Julie Gralow, MD, Protocol Chair
Email: pink@u.washington.edu

NCIC-Clinical Trials Group

Debjani Grenier, MD, Protocol Chair

CALGB-40101/NSABP-B-36

Cancer and Leukemia Group B

Lawrence Shulman, MD, Protocol Chair
Tel: 617-632-2277; 866-790-4500
Email: Lawrence_Shulman@dfci.harvard.edu

National Surgical Adjuvant Breast and Bowel Project

Richard Elledge, MD, Protocol Chair
Tel: 713-798-1655

Email: relledge@bcm.tmc.edu

SWOG-S0221**Southwest Oncology Group**

George Budd, MD, Study Coordinator
Tel: 216-444-6480; 800-862-7798

Email: S0221@cc.ccf.org

Halle Moore, MD, Study Coordinator
Tel: 216-445-4624; 800-862-7798

NSABP-B-38**National Surgical Adjuvant Breast and Bowel Project**

Sandra Swain, MD, Protocol Chair
Tel: 301-496-0901

ECOG-E2104**Eastern Cooperative Oncology Group**

Kathy Miller, MD, Protocol Chair
Tel: 317-274-0920; 888-600-4822

Email: kathmill@iupui.edu

Robin Zon, MD, Protocol Co-chair

Tel: 574-234-5123

North Central Cancer Treatment Group

Edith Perez, MD, Protocol Chair
Tel: 507-284-1159

Email: perez.edith@mayo.edu

NCT00121134**Dana-Farber/Harvard Cancer Center at Dana-Farber Cancer Institute****Beth Israel Deaconess Medical Center**

Harold Burstein, MD, PhD, Principal Investigator
Tel: 617-632-6767

Metastatic Disease**SoFEA****Institute of Cancer Research — Sutton**

Stephen Johnston, MD, PhD, FRCP
Protocol Chair

Tel: 44-20-7808-2745

Email: stephen.johnston@rmh.nhs.uk

SWOG-S0226**Southwest Oncology Group**

Rita Mehta, MD, Study Coordinator
Tel: 714-456-5153

NCIC-Clinical Trials Group

Theodore Vandenberg, MD, Protocol Chair
Tel: 519-685-8640

FACT**AstraZeneca Pharmaceuticals LP**

Roger Henriksson, MD, Study Director

AstraZeneca Clinical Study Information

Tel: 46-(0)8-553-26000

CONFIRM TRIAL**AstraZeneca Pharmaceuticals LP****AstraZeneca Cancer Support Network**

Tel: 866-992-9276

EGF104383**GSK Clinical Trials**

See the NCI Physician Data Query at

cancer.gov/search/clinical_trials/

for participating sites

EGF104900**GSK Clinical Trials**

See the NCI Physician Data Query at

cancer.gov/search/clinical_trials/

for participating sites

CALGB-40503**Cancer and Leukemia Group B**

Maura N Dickler, MD, Principal Investigator

Matthew J Ellis, MD, PhD, Principal Investigator

UCLA-0502057-01**Jonsson Comprehensive Cancer Center at UCLA**

Richard Pietras, MD, PhD, Protocol Chair

Tel: 310-825-9769, 888-798-0719

Email: rpietras@ucla.edu

RIBBON 1/RIBBON 2**Ribbon 1: Genentech Incorporated**

Barbara J Hencke, MD, Study Director

Genentech Trial Information Support Line

Tel: 888-662-6728

Ribbon 2: Genentech Incorporated

Julie Hambleton, MD, Study Director

Genentech Trial Information Support Line

Tel: 888-662-6728

QUESTIONS (PLEASE CIRCLE ANSWER):

1. TAILORx will randomly assign patients with a(n) _____ recurrence score, according to the Oncotype DX assay, to hormonal therapy alone versus hormonal therapy combined with chemotherapy.
 - a. High
 - b. Intermediate
 - c. Low
 - d. All of the above
2. Which of the following treatments are being compared in the SoFEA trial?
 - a. Exemestane
 - b. Fulvestrant
 - c. Fulvestrant with anastrozole
 - d. Both a and b
 - e. a, b and c
3. In the randomized trial SWOG-S0221, which schedule of AC requires growth factor support?
 - a. Metronomic
 - b. Dose dense
 - c. Both a and b
4. Which of the following treatments are being compared in SWOG-S0226?
 - a. Anastrozole
 - b. Fulvestrant
 - c. Fulvestrant with anastrozole
 - d. Both a and c
 - e. a, b and c
5. NSABP-B-35 compares _____ to tamoxifen as adjuvant therapy for postmenopausal women with ER-positive DCIS.
 - a. Raloxifene
 - b. Exemestane
 - c. Anastrozole
 - d. Letrozole
 - e. Fulvestrant
6. The CONFIRM trial compares the 250-mg versus the 500-mg dose of fulvestrant in postmenopausal women with advanced breast cancer.
 - a. True
 - b. False
7. The ACOSOG-Z1031 trial is evaluating which of the following agents as neoadjuvant endocrine therapy?
 - a. Anastrozole
 - b. Letrozole
 - c. Exemestane
 - d. All of the above
8. In the six arms of the neoadjuvant trial NSABP-B-40, three chemotherapy regimens are compared with or without the addition of _____.
 - a. Bevacizumab
 - b. Trastuzumab
 - c. Lapatinib
 - d. Gefitinib
9. In the NSABP-B-38 trial comparing TAC versus dose-dense AC followed by paclitaxel versus dose-dense AC followed by paclitaxel/gemcitabine, primary prophylaxis with pegfilgrastim or filgrastim is not required.
 - a. True
 - b. False
10. The Phase III trial, EGF104900, compares lapatinib with or without _____ in women with HER2-positive, metastatic breast cancer.
 - a. Capecitabine
 - b. Docetaxel
 - c. Paclitaxel
 - d. Trastuzumab
11. The proposed APHRODITE trial (BIG-2-06) compares monotherapy, concurrent therapy and sequential therapy of which two agents?
 - a. Trastuzumab and paclitaxel
 - b. Trastuzumab and anastrozole
 - c. Trastuzumab and lapatinib
 - d. Trastuzumab and bevacizumab
12. Trials evaluating endocrine therapy in premenopausal patients include _____.
 - a. SOFT (IBCSG-24-02)
 - b. TEXT (IBCSG-25-02)
 - c. PERCHE (IBCSG-26-02)
 - d. All of the above
13. The NSABP-B-39 trial is comparing whole breast irradiation to _____ in patients with DCIS or Stage I/II breast cancer.
 - a. No radiation therapy
 - b. Partial breast irradiation
 - c. Endocrine therapy
14. The proposed CALGB-40503 trial evaluates _____ in combination with endocrine therapy for patients with metastatic disease.
 - a. Trastuzumab
 - b. Capecitabine
 - c. Gemcitabine
 - d. Bevacizumab

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor N/A = Not applicable

GLOBAL LEARNING OBJECTIVES

To what extent does this issue address the following global learning objectives?

- Describe ongoing and planned clinical trials in the adjuvant, neoadjuvant and metastatic settings and counsel appropriately selected patients about the availability of ongoing clinical trials. 5 4 3 2 1 N/A
- Explain hormonal therapy treatment strategies currently under evaluation for both pre- and postmenopausal patients with ER-positive breast cancer. 5 4 3 2 1 N/A
- Describe the rationale for and design of ongoing clinical trials of various chemotherapeutic agents, including trials evaluating dose-dense chemotherapy regimens. 5 4 3 2 1 N/A
- Evaluate treatment strategies combining biologic agents with chemotherapy, endocrine therapy and other biologic agents in planned and ongoing clinical trials. 5 4 3 2 1 N/A
- Discuss the utility of genomic markers as a tool for determining whether to administer chemotherapy in combination with hormonal therapy for postmenopausal patients with ER-positive breast cancer. 5 4 3 2 1 N/A
- Describe the results of the large clinical trials evaluating adjuvant trastuzumab in patients with HER2-positive breast cancer as a model for future clinical research. 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Julie R Gralow, MD	5 4 3 2 1	5 4 3 2 1
Clifford Hudis, MD	5 4 3 2 1	5 4 3 2 1
Edith A Perez, MD	5 4 3 2 1	5 4 3 2 1
John F R Robertson, MD	5 4 3 2 1	5 4 3 2 1
George W Sledge Jr, MD	5 4 3 2 1	5 4 3 2 1
Norman Wolmark, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

- Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1 N/A
- Related to my practice needs. 5 4 3 2 1 N/A
- Will influence how I practice. 5 4 3 2 1 N/A
- Will help me improve patient care. 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. 5 4 3 2 1 N/A
- Overall quality of material. 5 4 3 2 1 N/A
- Overall, the activity met my expectations. 5 4 3 2 1 N/A
- Avoided commercial bias or influence. 5 4 3 2 1 N/A

Which of the following audio formats of this program did you use?

- Audio CDs Downloaded MP3s from website

Evaluation Form

REQUEST FOR CREDIT — please print clearly

Name: Specialty:

Degree:

MD DO PharmD NP BS RN PA Other

Medical License/ME Number: Last 4 Digits of SSN (required):

Street Address: Box/Suite:

City, State, Zip:

Telephone: Fax:

Email:

Research To Practice designates this educational activity for a maximum of 4 AMA PRA Category 1 Credit(s)TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: Date:

Will the information presented cause you to make any changes in your practice?

Yes No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

FOLLOW-UP

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

Yes, I am willing to participate in a follow-up survey.

No, I am not willing to participate in a follow-up survey.

SABCSWB06 **To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at BreastCancerUpdate.com/ClinicalTrials/CME.**

Breast Cancer Clinical Trials Resource Guide and Audio Program

Editor/CME Director	Neil Love, MD
Managing Editor	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Writers	Lillian Sklaver Poltorack, PharmD Douglas Paley
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng Ginelle Suarez Erin Wall
Director, Creative and Copy Editing	Aura Herrmann
Creative Manager	Fernando Rendina
Graphic Designers	Jason Cunnius Tamara Dabney Shantia Daniel Elisa Stambouli
Senior Production Editor	Alexis Oneca
Managing Production Coordinator	Tere Sosa
Copy Editors	Dave Amber Mary DiNunzio Rosemary Hulce Kirsten Miller Pat Morrissey/Havlin Carol Peschke Susan Petrone
Production Manager	Patricia Kappes
Audio Production	Frank Cesarano
Technical Services	Arly Ledezma
Web Master	John Ribeiro
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

Copyright © 2006 Research To Practice. All rights reserved.

This program is supported by education grants from Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech Inc and Genomic Health Inc.

The compact discs, internet content and accompanying printed material are protected by copyright. No part of this program may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or utilizing any information storage and retrieval system, without written permission from the copyright owner.

The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management.

Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

Breast Cancer[®]

U P D A T E

Copyright © 2006 Research To Practice.
This program is supported by education grants from
Amgen Inc, AstraZeneca Pharmaceuticals LP,
Genentech Inc and Genomic Health Inc.



Sponsored by Research To Practice.

Last review date: December 2006
Release date: December 2006
Expiration date: December 2007
Estimated time to complete: 4 hours